PHYSIOLOGICAL PRINCIPLES IN TREATMENT

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PREFACE TO THE FIFTH EDITION

THAT yet another edition of this book should be called for is naturally gratifying to the author. Its preparation has been delayed partly by the pressure of other work, but also because rapid advances in the subjects dealt with have made extensive revisions necessary. This is particularly the case with the biochemical sections.

Two new chapters have been added—one on the work of the liver, the other on asthma. New sections have also been added on fractional test meals, insulin, uræmia, and dyspnœa. In accordance with the recommendations of the Medical Research Council, the nomenclature in Chapter X. has been altered.

I should like gratefully to acknowledge the kindly criticisms which former editions received in the medical press and private letters, and I have gladly availed myself of many of the suggestions contained therein. It is my pleasant duty to express my thanks to Professor Lovatt Evans and Dr. R. Hilton for useful help and suggestions in the preparation of this edition.

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FROM THE PREFACE TO THE FIRST EDITION

In the last decade our ideas have undergone fundamental alterations on many points of cardinal importance in physiology. The same period has seen a much wider use of exact scientific methods in clinical work. The result has been a closer harmony between physiology and practical medicine. The researches of Pavloff and his followers, which have led to the rewriting of the physiology of digestion, the clinical applications of Gaskell's work on the heart by Mackenzie and others, the introduction of convenient methods of registering blood-pressure in man, the increased knowledge of the chemistry of uric acid and its congeners, of nitrogenous metabolism and internal secretion, are examples which will occur to anyone.

The busy practitioner is aware that the physiology of his student days has been largely supplanted or supplemented, but has not time to acquaint himself with the changes, nor to deduce therefrom the points on which his clinical conceptions should be modified.

This book does not aim at being a complete treatise on applied physiology; but as it has been my lot during the decade in question to combine the practice of medicine with the teaching of physiology, I have set down

here some of the considerations which I think have helped me, in the hope that they may help others. . . .

Though the days are past when the student entering the wards often received the superfluous advice to 'forget his physiology,' the physiologist is still regarded a little suspiciously at the bedside. Perhaps he is in part himself to blame for that, for he is sometimes inclined to forget that observations made in the laboratory are not infallible, and are not necessarily more correct than clinical evidence. When I reflect that I am now teaching the exact opposite to many of the views held ten years ago, I feel that physiology can only come to the aid of medicine with becoming modesty, and without overweening dogmatism. There is no finality about either, but that they can co-operate usefully I trust the following pages serve to illustrate.

W. LANGDON BROWN.

October, 1903.

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PHYSIOLOGICAL PRINCIPLES IN TREATMENT

CHAPTER I

THE PRINCIPLES OF ORGANO-THERAPY

WHENEVER we give a drug, we imply thereby a belief that the functions of the body can be influenced by chemical means. And we can find support for this confidence in the fact that the body itself produces chemical substances whereby it regulates its own functions.

Nothing could be more reasonable than to use intelligently in disease those very drugs by which the body is enabled to do its own work in health. This is the basis of a rational organo-therapy, as Starling has so clearly indicated.

Though the use of organic extracts has enormously increased during recent years, it is but the renaissance of a very ancient method. Celsus and Galen testify to the antiquity of organo-therapy. The first Pharmacopœia, published by the College of Physicians

in 1618, contains several preparations of animal extracts.

The success of thyroid extract in treatment led to a great revival of interest in the subject, an interest not always intelligently displayed. Indiscriminate use of gland extracts in every sort of disease, without consideration of the underlying principles, only brings discredit on a valuable method of treatment. There is no scientific sanction for the employment of brain extract in insanity, and extracts of bronchial glands for phthisis. Powdered heart muscle was a favourite prescription in the old days; it is no advance to squeeze it into a tablet and call it cardin.

In the past it has been too much the fashion to look upon the different organs as largely independent of each other, though under the suzerainty of the brain. But the development of a nervous system is a comparatively late event in evolution. The stimuli to which the most primitive forms of life respond are chemical; the nervous system enables very rapid reactions to occur, but where less sudden responses are needed the primitive method is retained.

Thus, salivary secretion may occur before the food enters the mouth; and though gastric secretion is started by the taste of the food, its continuance is due to chemical stimuli, while pancreatic secretion can be explained by chemical factors alone. Here we note a gradual transition from a nervous to a chemical method of stimulation, as the need for rapidity of response grows less. This is a good example of the

way in which the nervous system may start a series of events, though the subsequent chapters are due to chemical interactions, one organ producing a chemical substance necessary as a stimulant to the next in series.

For these substances Starling suggests the name hormones' (ὁρμαω, 'I excite'). Internal secretions owe their activity to hormones.

The chemical products of every organ must influence the rest of the body to some extent, but it is only when that influence is specific that we dignify the product with the status of a hormone. Thus, carbon dioxide is a product of all the tissues, but has a specially stimulating effect on the respiratory centre, while kreatin, which is formed by muscular tissues, increases gastric secretion and stimulates growth. Such reactions differ in degree rather than in kind from those of thyroxin and adrenalin. We may regard the endocrine glands as structures for elaborating chemical stimulants which were formerly more widely diffused throughout the body. In the course of evolution they have gradually come to a greater or less extent under the control of the lowest level of the nervous system.

Abrahams classified thus the inherent apparatus by which the body can defend itself when attacked:

1. *The physiological reserve,* primarily to combat exhaustion. This is called up in any condition of unusual strain, cardiac hypertrophy being a typical example.

2. *The biochemical apparatus*, which enables one tissue, when attacked, to appeal to another for assistance.

3. *The nervous mechanism*, which, as we have seen, is the latest in evolution, and the swiftest and most complex in its action.

The most essentially vital acts are subserved by a double mechanism. Thus, in heart diseases it is to the physiological reserve and the nervous mechanism that we look, while in digestive disturbances we must rely on the biochemical apparatus and the nervous system. In organo-therapy we are calling the biochemical apparatus to our aid.

Now, the substances which produce effects upon the body fall into two groups (Ehrlich). The first are closely allied in their chemical character to proteins, such as the toxins; all are produced by the agency of living organisms. As a result of their introduction, the tissues react by development of an antibody, and they are therefore called 'antigens.' The second group include all the common drugs, which probably act on protoplasm by reason of their molecular configuration, producing their effect, without any incubation period, as soon as they reach the cells. Although repeated doses can set up a certain degree of tolerance, they do not appear to rise to the production of an antibody.

Hormones resemble the second class, though when they are present in excess they sometimes seem capable of exciting the production of an antibody. They

belong to the permanent, and not to the acquired, defences of the body, and it has been suggested that in many instances drugs produce their effect by acting through the endocrine glands.

The general features of hormones may be stated thus:

1. They are bodies of comparatively small molecular weight.

2. Unlike ferments, they are not destroyed by simple heating, but may lose power on prolonged boiling.

3. They are rapidly destroyed by oxidizing agents.

4. They are destroyed in the tissues which they excite, and do not escape in any of the excretions.

5. They are not readily absorbed unaltered from the alimentary canal. Thyroxin, the active principle of thyroid extract, is an exception to this rule, probably because the thyroid gland originally discharged its secretion into the alimentary canal by the thyro-glossal duct. For a similar reason the secretion of the anterior lobe of the pituitary might be expected to be absorbed by this route, and there is some evidence that this is true even of the secretion of the posterior lobe. But the process is by no means so certain as in the case of the thyroid. Recent work suggests that pituitrin is more readily absorbed from the nasal mucosa.

Hormones are employed in treatment—

1. In substitution therapy—*i.e.*, to replace the absent or deficient secretion of a gland that is involved in a destructive lesion—or where there is relative insufficiency owing to overaction of some antagonistic gland.

Here the hormone is intended to produce a chronic effect.

2. Where their known physiological action may be useful quite apart from any defect in the patient's own glands. Here a sudden effect is usually aimed at.

3. In a purely empirical manner.

For successful substitution therapy the gland from which the extract is prepared must contain the hormone in an amount much in excess of the body's immediate needs, while the hormone must be fairly stable so as to resist chemical changes during extraction, and be capable of absorption from the alimentary canal. Also it must be possible for intermittent doses to replace satisfactorily the constant slow secretion which normally occurs. As Dale points out, the thyroid is the only ductless gland which fulfils all these criteria. For the rest the principal successes have been confined to conditions where the hormone can be used locally or by injection, and where a sudden rather than a prolonged effect is required. Fortunately, hormones are not destroyed by boiling, so they can be prepared in sterile solutions suitable for injection.

The Thyroid Gland and Thyroxin.

Organo-therapy won its first and most conspicuous triumph with thyroid extract. The ease with which thyroid preparations are absorbed from the alimentary canal has greatly contributed to this, but at the outset it was not realized that so simple a method

could be effective, and subcutaneous injections were employed.

The only active principle that has been isolated from the gland is thyroxin, which Kendall showed to be an iodine compound of indol. The presence of iodine, which is a striking peculiarity of this hormone, is interesting, in view of the empirical use of iodine in diseases of the thyroid. It certainly appears to allow the gland to return to a resting state, and its use as a prophylactic in districts where goitre is endemic, such as certain Swiss valleys, has been very successful. Such a method may also prevent the body drawing on its emergency ration of iodine in the form of thyroxin, which may have other and injurious effects.

The thyroid gland is to the human body what the draught is to the fire (McCarrison). It is a general accelerator of metabolism and growth; this has been demonstrated mathematically by observations on the basal (*i.e.*, resting, fasting) metabolism.

Thyroxin has the effect of reducing weight, but it has been stated that only one-sixth of the loss is due to increased nitrogenous waste, the remainder being due simply to diuresis, apparently from dehydration of fats. It lowers sugar tolerance and may produce glycosuria. It accelerates the heart-beat without augmenting its force. It is therefore not very effective in the treatment of ordinary obesity, and is not free from risk, as a fatty heart may not be able to maintain the accelerated rhythm. Moreover, as in obesity there is often a tendency to glycosuria, the use of a drug

which can excite this demands caution. But if the obesity is associated with other signs of hypothyroidism, careful administration of thyroid extract may be very helpful.

From its great success in myxœdema and cretinism, we may regard thyroxin as a hormone with a special action on the central nervous system and on the skin and subcutaneous tissue. These points are generally familiar. The occasional failures in the treatment of myxœdema may be explained thus:

1. In persons of advancing years thyroxin appears to have less effect.

2. As subjects of myxœdema are more liable to those toxic symptoms known as thyroidism, it is not always possible to give an adequate dose.

While failures in the treatment of cretinism may be accounted for as follows:

1. Successful treatment is only possible before the degeneration of the brain consequent on cretinism has occurred.

2. Errors in diagnosis have led to Mongolian idiots and achondroplasics being treated as cretins.

Cretinism is more apt to occur when the mother has a thyroid which is below normal standard. Thyroxin passes readily into the mother's milk.

Hertoghe points out that the thyroid (*a*) governs the building up of the cells and (*b*) regulates the destruction of the protein molecule and its elimination. Therefore with thyroid insufficiency there will be defective growth, which will be most noticeable in the young

subject, while in the adult there will be accumulation of material which should be katabolized. He attributes to a minor degree of thyroid insufficiency such symptoms as relaxation of the articular ligaments, particularly in the knee, heel, ankle, and thoracic vertebræ, causing knock-knee, painful heel, flat-foot, and lordosis. Infiltration of tendons and fascia may produce rheumatoid pains. He attaches considerable importance to the loss of hair in the outer half of the eyebrow. Enuresis he believes to be frequently due to the same cause. Thyroid inadequacy diminishes the coagulability of blood, which explains the tendency to hæmorrhage. Infiltration of the nerve centres causes mental slowness, partial or entire loss of memory, and difficulty in expressing ideas. Sometimes there are hallucinations of sight and hearing. Headache, giddiness, and somnolence are not uncommon. The liability of myxœdematous subjects to develop atheroma suggests the use of thyroid extract in premature arterial degeneration. Leonard Williams maintains that in all such conditions the doses usually employed are far too large. He begins with half a grain twice a day and never increases the dose to a point sufficient to cause tachycardia.

The striking changes occurring in the skin in myxœdema implies that the thyroid plays an important part in regulating its nutrition. Byrom Bramwell therefore employed thyroid extract in various diseases of the skin. The best results seem to have been obtained in psoriasis, ichthyosis, and lupus vulgaris. Its use should be

restricted to chronic conditions; Radcliffe Crocker finds that it may excite new lesions if given while the eruption of psoriasis is still developing.

As fractures have been found to heal better in thyroidectomized animals if thyroid extract be given, it has been used to hasten the union of fractures in normal individuals, apparently with benefit. Hertoghe is inclined to think, however, that such individuals have a minor degree of thyroid insufficiency. Occasionally the extract appears to delay the growth of a cancer of the breast.

Among the less-known effects of thyroxin on metabolism is its influence on the liver. Apart from the discoloration, the chief sufferings of a jaundiced patient are due to the toxic effects of the bile-salts; prominent among these is the intense itching, which is sometimes so troublesome.

After ligature of the bile-duct the colloid in the follicles and lymphatics of the thyroid gland increases. Possibly this is a defensive step against intoxication by bile-salts, and accordingly Gilbert and Herscher administered thyroid extract to seven cases of jaundice; in six the pruritus was benefited.

Under thyroid treatment the bile-salts in the urine gradually diminished and then disappeared. After cessation of treatment the reaction returned until thyroid extract was again administered. They concluded that thyroid extract must modify or destroy the bile-salts. Outside the body they did not find that thyroid has any effect on bile-salts.

Employing Leyton's method of estimating bile-salts, I have been able in several cases to confirm Gilbert and Herscher's statement that the administration of thyroid extract diminished the amount of bile-salts in the urine, with great relief of pruritus. I have also found that feeding a cat with thyroid gland diminished its production of bile-salts.

In eclampsia thyroid extract has been advocated, on the ground that in normal pregnancy an enlargement of the thyroid gland occurs, while in the albuminuria of pregnancy or in eclampsia this enlargement may be lacking. As some effect on hepatic metabolism must be conceded to the thyroid, and as some hepatic lesion is responsible for eclampsia, there is a rational basis for this plan of treatment.

The striking contrast between Graves' disease and myxœdema suggests naturally that while the latter is due to an athyrea, the former is associated with a hyperthyrea. In Graves' disease the gland is enlarged by an increase in the secreting cells, the excitability of the nervous system in increased, the pulse is rapid, the temperature is raised, the skin is moist, the basal metabolism is increased, and there is usually emaciation. In myxœdema the gland is atrophic, the excitability of the nervous system is diminished, the pulse is slow, the temperature subnormal, the skin dry, while diminished basal metabolism and increase of weight are the rule. Moreover, the administration of excessive doses of thyroid extract may cause symptoms analogous to those of Graves' disease. Since thyroxin

is a hormone acting on the skin and nervous system, Graves' disease could be explained by a hyperthyrea in which the emotional centres undergo an excessive stimulation. Hector Mackenzie has drawn attention to the resemblance between the symptoms of Graves' disease and the expression of the emotion of fear. In both we have the staring eyes, the rapid pulse, and the tremors. It is doubtful, however, whether the phenomena of Graves' disease are all due to a primary hyperthyrea. Indeed, hyperthyrea may be produced by stimulation of the sympathetic, and I am convinced that a continued emotional disturbance plays a large part in the production of Graves' disease, especially when combined with a toxic factor. Myxœdema following Graves' disease we can understand, for the gland may become exhausted as a direct result of its excessive activity; but the coexistence of active Graves' disease with some of the symptoms of myxœdema, such as the characteristic condition of the skin, is more difficult to account for. ~~Rothschild and Leopold-Levi~~ attribute this to thyroid instability. There is an irritable weakness of the gland which causes spurts of hyperthyroidism, in spite of a constant basis of hypothyroidism.

In view of these facts the failure of organo-therapy in Graves' disease is hardly surprising. Thus, if the disease is associated with hyperthyrea, administration of thyroid extract could do, and usually does, nothing but harm. Where there has been a compensatory enlargement of the thyroid consequent on some extra

demand for thyroxin, small doses of thyroid do good. But these are not cases of Graves' disease and are accompanied by some signs of thyroid insufficiency. Thus, in a cretin I saw a cystic enlargement of the gland disappear under thyroid extract.

The other organo-therapeutic measures that have been tried are antitoxic and cytolytic. The hypothesis on which the former method rests is that the blood of a thyroidectomized animal should contain an excess of substances unneutralized by thyroid secretion; these should be antagonistic to a hypertrophied thyroid. But the proof that such substances occur is not satisfactory, and the hypothesis implies an antitoxic rather than a secretory function for the thyroid.

As the rational basis for the use of such preparations is so uncertain, we need not be surprised at the lack of success that has attended the use of Rodagen, Antithyroidin, and Thyroidectin. Lanz and Edmunds have reported benefit from the use of the fresh milk of thyroidectomized goats.

The trial of thyrolytic serum is based on the well-known fact that if a preparation of the cells of one animal be repeatedly injected into the circulation or peritoneal cavity of another animal, the latter will form an antibody capable of destroying those introduced cells. This method has been abandoned as it is ineffective and risky.

The Parathyroids.—Recent work has thrown new light on the function of the parathyroids. In 1907 Forsyth concluded, after careful study, that the

parathyroids are portions of the main thyroid gland which have not yet formed vesicles, that all the intermediate stages between thyroid and parathyroid tissues occur: and that they were essentially similar in function. Dunhill, however, believes that parathyroids can be histologically recognized. James Berry states that, although he has removed goitres 1,338 times, he has never seen tetany develop, although he takes no special care to avoid the parathyroids. He admits, however, that he leaves a piece of gland at the hilus, and may therefore have preserved them. On the other hand, Noel Paton and Findley in 1916 observed muscular spasms and tremors after experimental removal of the parathyroids with the thyroid in animals. Of late the tendency has been to attribute two definite functions to the parathyroids (1) to destroy guanidine, a purin body which otherwise accumulates in the muscles, where it is believed to cause tetany; (2) to increase the ionizable calcium content of the blood. The first effect has been used by Vines to estimate the activity of preparations claimed to contain parathyroid secretion, and the second has been proved by the same observer by direct estimation of the calcium content of the blood.

As calcium salts are sedative in their effect on the nervous tissues, the association of parathyroid defect with tetany has been referred to this as well as to the accumulation of guanidine in the muscles. Thus, Howland and Marriott found the normal calcium content of the serum to be 10 or 11 milligrams per cent.

This was invariably reduced during active tetany to an average of 5·6 milligrams, but not in other convulsive disorders. They maintained that administration of calcium salts promptly checked the spasms and caused a rise in the calcium content of the blood. Other observers have found parathyroid extract more effective. Hurst, in 1915, reported a case of fibrillary twitchings, tremors, and diarrhœa coming on two years after removal of the greater portion of the thyroid, which was aggravated by thyroid extract but greatly benefited by $\frac{1}{10}$ grain of parathyroid extract four times a day. G. H. Clark described three cases in children of idiocy, depression, fibrillary twitchings in the muscles, jerking movements of the limbs, convulsions and inability to balance. Struck with the resemblance to the condition produced in animals by removal of the parathyroids with the thyroid, he treated them with parathyroid extract with remarkable benefit. On discontinuing the drug the symptoms returned, in one case on two occasions.

Korenchevsky has produced tetany in rats by destroying the large parathyroid embedded in the thyroid with the electric cautery. Parathyroid extract has been given for many nervous conditions associated with twitchings and tremors. It appeared to benefit a case of myoclonic movements following encephalitis in a child under my care. Grove and Vines found in the case of lesions that could be directly observed, such as a varicose ulcer on the leg, that parathyroid extract was capable of raising the calcium content of the blood

to normal, and that this was followed by speedy healing. They then applied this method to internal lesions, such as gastric and duodenal ulcers, with similar results. They believe that calcium deficiency is an index of the absorption of a toxin, and that in all the disease improved by parathyroid therapy the common factor is sepsis. The dose is $\frac{1}{8}$ of a grain twice a day, or $\frac{1}{10}$ of a grain thrice a day. In view of the striking clinical benefits claimed by numerous observers by parathyroid treatment, it would be rash to assume that these bodies have no separate function.

The Suprarenals and Adrenalin.

Following on Addison's clinical observations, Brown-Séquard showed that experimental removal of the suprarenals was rapidly fatal to animals. Schäfer and Oliver in 1893 prepared from these glands an active substance possessed of powerful tonic properties. That this substance was only formed from the medulla of the gland was shown by Swale Vincent from observations on certain fishes in which the cortical and medullary portions are separate glands. Attempts to isolate the active principle from the extract culminated in 1901 in the preparation by Takamine of a crystalline body, to which he gave the name of adrenalin, and to which he attributed the formula $C_{10}H_{15}NO_3$. This name has now been adopted by the British Pharmacopœia.

Four years later Dakin synthesized it artificially from pyrocatechin, and made a series of similar bodies, showing that their activity depended on the presence of

a catechol nucleus. This suggests an origin from the aromatic radicles present in the protein molecule.

We owe to Langley the important generalization that the action of adrenalin on any part is the same as stimulation of the sympathetic nerves to that part. It will not act on a structure that at no time in its history has been innervated by the sympathetic. Elliott, in extending these observations, has brought forward some facts which suggest that, after excision of the suprarenals, the muscles innervated by the sympathetic cannot be thrown into activity even by electrical stimulation of the nerves. Adrenalin appears, then, to be a chemical body whose presence is essential to the activity of the sympathetic. This is specially interesting, when we remember that the medulla of the suprarenal gland is developed as a direct outgrowth from the sympathetic nervous system. Nor is this the only example of such an association, for sympathetic paraganglia and structures, such as the carotid body, contain *paragangline*, a similar but more stable body, which does not lose its effect even if left in contact with the stomach wall for twenty-four hours.

In applying adrenalin therapeutically we have to consider what would be the effect of stimulating the sympathetic nerves to the part in question. Whether it acts on a 'myoneural junction,' as suggested by Elliott, or on a 'receptive substance' in the cell, as Langley thinks, does not affect this conclusion. The application of adrenalin to internal medication is greatly limited by two facts:

1. If mixed with alkalies, its activity is lost; if the alkali be neutralized, the specific effect can be obtained again. Now, as the blood-stream is alkaline, it can only produce a brief general effect through the circulation.

2. It is doubtful whether in healthy persons it is absorbed unaltered from the alimentary canal. The most striking action of adrenalin is the rise of blood-pressure that it causes, but many observers have failed to detect any rise when the drug has been given by the mouth. Yet it is not destroyed by gastric juice in a test-tube. Probably the intense vaso-constriction it produces prevents its own absorption. Rolleston found that, given by the mouth to persons suffering from Addison's disease, it did raise the blood-pressure, though I have often failed to obtain this result. In the same way a myxœdematous person is well known to be much more sensitive to thyroid extract than a healthy individual. Schäfer thinks that injured vessels are similarly more sensitive to adrenalin than normal ones, and that a selective vascular constriction may be thus produced even though no general rise of blood-pressure occurs.

It will follow that the drug is most effective when it can be applied direct to the point at which we wish it to act. Even after subcutaneous injection its general effect is much interfered with by the local constriction of bloodvessels, which prevents its entering the circulation until its activity has passed off.

Alimentary Canal.—Since Leyton suggested supra-

renal extract for hæmatemesis, many instances of its successful use have been reported. I place considerable reliance on ½-drachm doses of the 1 in 1,000 solution of adrenalin chloride in ½ ounce of water, given every three or four hours. Elliott recommends adrenalin borate $\frac{1}{32}$ or $\frac{1}{64}$ grain for hypodermic use, the chloride being painful. In addition to constricting the bleeding-point, it stops peristalsis. If an isolated loop of intestine be placed in a bath of warm salt solution, vigorous peristaltic waves may be seen; the addition of two or three drops of adrenalin solution to the bath at once renders the coil quiescent. Like the sympathetic, adrenalin inhibits the movement of a hollow viscus, while keeping the sphincter controlling the exit closed. Herein lies its advantage over ergotin and the like. For these reasons it will often check vomiting or hiccough, in doses of 10-15 minims of the 1 in 1,000 solution diluted with water. I have found this most useful in combination with 1 minim of carbolic acid and 3 minims of dilute hydrocyanic acid.

It may be tried in intestinal hæmorrhage, though it is open to doubt whether the drug can get past the pyloric sphincter. Graeser succeeded in checking severe intestinal bleeding in typhoid fever by giving three hourly doses of 30 minims of the solution by mouth where ice, opium, ergot, and bismuth had all failed. I have used it in this way with satisfactory results. It may be added also to an enema of starch and opium. As a precautionary measure I have given a similar dose about a quarter of an hour before

getting the bowels opened by enema after an intestinal hæmorrhage. By keeping the bloodvessels of the small intestine constricted, the walls flaccid, and the ileo-cæcal sphincter closed, it affords the ideal condition for emptying the large bowel by enema.

In view of the inhibitory action of adrenalin on peristalsis, it is contra-indicated in the treatment of gastro-intestinal atony.

Exner found that intraperitoneal injection of adrenalin delays the absorption of poison introduced into the stomach or peritoneal cavity; thus strychnine required twenty times as long to produce its toxic effect. This gain of time is most valuable, and suggests the administration of a full dose of adrenalin pending the employment of other remedies.

Heart and Bloodvessels.—Adrenalin is a powerful stimulant to the heart, augmenting its action like the sympathetic; but, as we have seen, to produce this effect it must be injected intravenously. We must remember, however, that as it also constricts the bloodvessels, thereby raising the pressure, it may stimulate the cardio-inhibitory centre in the medulla, so that slowing of the heart through the vagi might be caused instead. Though this might perhaps be prevented by simultaneous injection of atropin, this would merely mean that a way of escape from the excessive pressure would be barred. The sudden vaso-constriction greatly increases the work of the heart, and if this cannot be met dilatation of the cavities may occur. Dilatation and vagal inhibition are dangers

that would outweigh any advantage to be derived from the stimulating effect of the adrenalin. The safest thing to do is to give amyl nitrite at the same time, unless the blood-pressure is already low; this will flush the peripheral vessels, thus avoiding the extra work and the stimulation of the cardio-inhibitory centre, though not entirely eliminating the rise of pressure. The action of both drugs is about equally sudden and transitory. I regard 3-5 minims as a large enough dose to give intravenously at one time. Fortunately, it has been shown experimentally that adrenalin does not constrict the coronary vessels, for if it did it would almost certainly produce anginal attacks. In cases of shock, where the blood-pressure is lowered from dilatation of the splanchnic bloodvessels, adrenalin is free from these risks, so that the amyl nitrite is unnecessary. And 'heart failure' in toxæmia is often partly due to vasomotor paralysis, so that adrenalin may be very useful in such cases, if its mode of action is duly borne in mind. I have seen great improvement follow intravenous injections for the collapse of toxæmic states, especially pneumonia, as Rolleston has found. Elliott and Tuckett observed that in diphtheria the chromogen in the medulla is deficient and this has been confirmed in other toxæmic states, which renders its action intelligible.' Crile found experimentally that in the most profound shock it was possible to keep up blood-pressure and maintain life by continuous intravenous infusion of adrenalin in salt solution, 1 in 50,000 to 100,000. In the collapse of chloroform or opium

poisoning it has also been found useful, though not permanent in its action. Recent observations on the paralysis of the capillary vessels in profound shock account for its lack of complete success.

Butler has recorded an example of its striking success in syncope after the crisis of pneumonia in a child of ten. He injected 38 minims in all in five doses, besides giving 10 minims by the mouth. He reported a significant fact, however: the immediate effect was an increase of pallor and a weakening of the pulse, followed by great and rapid improvement. Evidently, in the doses here used the immediate rise of blood-pressure was enough to act on the cardio-inhibitory centre in the way I have pointed out.

In accordance with the general law that adrenalin only acts on structures which have a sympathetic innervation, Baum found it had no effect in blanching nævi, and only a very transitory effect on unsound flesh.

Respiratory System. — A paroxysm of *asthma* may often be cut short by the subcutaneous injection of liq. adrenalin hydrochlor. In the first instance only 3 minims should be given, and it is rarely necessary to give more than 5 minims. It is still more effective if combined with pituitrin, and several preparations of the combined drugs are on the market. The vagus and sympathetic are opposed in their action, and as the former is constrictor in its effect on the bronchial muscles, the latter inhibits bronchial spasm; moreover, it constricts the turgid vessels in the bronchial mucosa. Both these actions would be produced by adrenalin.

In the chapter on the Vasomotor System in Disease, it is pointed out that the changes in the pulmonary circulation are passive, and are controlled by the systemic circulation. On perfusion of adrenalin through the pulmonary vessels Brodie and Dixon could not find any evidence of vaso-constrictors, a conclusion with which most subsequent observers have concurred. I have seen the thoracic viscera from an animal killed by a fatal dose of adrenalin; while all the other tissues were anæmic, the coronary vessels were distended with blood, and the lungs were intensely congested, being a deep plum colour. I therefore cannot believe that adrenalin is advisable in *hæmoptysis*. In so far as any result is obtained it will be a harmful one. The blood which is being squeezed out of the rest of the circulation will be forced into the pulmonary vessels, which are unable to protect themselves by adequate vaso-constriction, and hæmorrhage will be aggravated unless the sole source of the bleeding is a bronchial vessel. The only reason why serious harm has not been done more frequently is that the drug has been administered by the mouth, so that it has had little effect; but if injected into the circulation, it would have an injurious effect in hæmoptysis, because of the pulmonary engorgement that results.

Cerebral Hæmorrhage.—For similar reasons adrenalin is contra-indicated in cerebral hæmorrhage. Even admitting that there are vaso-constrictors in the vessels of the brain (and Wiggers found a slight constriction after perfusing adrenalin), the systemic rise of blood-pressure certainly outweighs any advantage to be

reaped from a possible local constriction in the cerebral vessels; and local application is out of the question.

In **hæmophilia**, adrenalin has been recommended but I have not been impressed with the results. Improvement has followed its use in **purpura**, though it is difficult to imagine how small doses of a drug which is probably not even absorbed from the stomach could affect hæmorrhages resulting from an altered condition of the blood. I have not been able to satisfy myself that the improvement was more than rest and suitable diet could account for. Dudgeon has suggested, however, that purpura may stand in the same relation to acute lesions of the suprarenals as pigmentation does to chronic destruction, a view which would make adrenalin the proper treatment. It is true that acute lesions of these structures such as hæmorrhage or necrosis are commonly accompanied by a purpuric eruption.

Serous Membranes.—Injection of adrenalin to prevent recurrence of ascites or pleural effusion has been advocated by Sir James Barr. A drachm of the adrenalin chloride solution with ½ per cent. of chloretone in 2 drachms or ½ ounce of sterilized water is injected through the trocar when the serous exudation has been withdrawn. Plant and Steele suggested that it acts by sticking the layers together, thereby promoting adhesions. I have seen abundant fibrous coagula in the peritoneal cavity post mortem following this treatment.

Surgical Applications.—Adrenalin has been very useful in certain surgical conditions, but on these I shall only touch briefly. For removal of foreign bodies and other operations on the eye, Darier recommends 10 drops of the 1 in 1,000 solution added to 10 c.c. of a *1 per cent. solution of cocaine. MacCallan thinks it is risky in glaucoma,* as he has seen it cause a rise in tension. I saw an alcoholic patient who was in the habit of dropping adrenalin into his eyes to diminish their bloodshot appearance, but the secondary reddening that followed the temporary constriction had left him in a worse plight than before.

Its blanching action has rendered adrenalin of considerable service both for diagnosis and treatment of diseases of the nose, for it is rapidly absorbed by the nasal mucous membrane. For similar reasons it is a palliative in hay fever.

In affections of the bladder it has been used with novocaine for anæsthetic purposes. Duncannon reports favourably on its use in catheterization in the pain and strangury of acute gonorrhœa, and in the hæmaturia of enlarged prostate. In the form of ointment it certainly seems to alleviate hæmorrhoids. In uterine bleeding it may be looked to to produce a double effect, constricting the bleeding vessels and causing contractions of the pregnant uterus. Cushing and Dale have shown the curious and interesting fact that adrenalin relaxes the non-pregnant and contracts the pregnant uterus. Such contractions are, however, inadequate to induce labour.

In local anæsthesia the role of adrenalin is to prevent the escape of the anæsthetic from the field of operation by constricting the bloodvessels in the neighbourhood. In this way its general toxic effect is diminished, while its local anæsthetic effect is increased. It has been proved experimentally that whereas of a subcutaneous injection of lactose one-third is excreted by the urine in the first hour, if two drops of liq. adrenalin hydrochlor. be added, none is excreted in that time, showing that it had not left the site of injection. In using adrenalin in this way it must be remembered that cocaine, novocaine, and alypin either have no influence on its action or slightly increase it; while eucaine, tropocaine, and possibly stovaine, are markedly antagonistic, considerably decreasing its activity.

It is important that there should be no trace of soda in the fluid used for boiling the syringe employed, since adrenalin is rapidly destroyed in alkaline solutions.

B. T. Lang recommends the following three solutions of different strengths, but all, as far as possible, isotonic with blood:

	A. 0·4 per Cent.	B. 0·8 per Cent.	C. 2 per Cent.
4 per cent. novocaine with 0·1 per cent. thymol with oil of gaultheria	1 c.c.	2 c.c.	5 c.c.
4 per cent. saline with thymol and oil of gaultheria	2 c.c.	2 c.c.	2 c.c.
1 in 1,000 adrenalin with thymol and oil of gaultheria ..	3 drops.	3 drops.	3 drops
Distilled water up to	10 c.c.	10 c.c.	10 c.c.

The most dilute solution is for fine nerve terminals; the larger the nerve trunks to be anæsthetized, the stronger should be the solution employed.

It is impossible to anæsthetize satisfactorily any inflamed tissue by immediate infiltration as the intercellular spaces are already filled with lymph, but it may be possible to attack the nerves supplying the inflamed area nearer the brain.

In spinal anæsthesia adrenalin is not so satisfactory, as it limits the spread of the injection too much. Also its use has been followed by petechial hæmorrhages in the brain, which may well be due to the blood being driven to a part which is unable adequately to protect itself by vaso-constriction.

Adrenalin and Addison's Disease.—Wilks' view of the 'unity of Addison's disease' now admits of restatement. We can reconcile the two views originally held as to its pathology—one ascribing it to fibro-caseous change in the suprarenals, the other to changes in the adjacent sympathetic—since the sympathetic cannot act in the absence of adrenalin.

Two of the cardinal symptoms of Addison's disease are now explained. As the sympathetic supplies accelerator fibres to the heart, and constrictor fibres to the bloodvessels, their paralysis must result in profound cardio-vascular atony. The sympathetic also provides the stomach with inhibitory fibres; their loss of function must lead to motor irritability of the stomach, and therefore to vomiting. This will be intensified because, the closure of the pyloric sphincter

being under the control of the sympathetic, regurgitation into the stomach can now easily occur from the duodenum.

The pigmentation is more difficult to explain. Adrenalin, like many other bodies containing the benzene nucleus, is a chromogenic substance, and Hopkins has suggested that the deposit of pigment is due to 'adrenalin gone wrong.' Some of the deposits of pigment have yielded a pressor substance, as if they were compensatory for adrenal defect. But in the main, I should agree with Rendle Short's view that the pigmentation results from the relaxed condition of the bloodvessels, like that produced by poulticing or exposure to light. The distribution of the pigmentation suggests this is the correct explanation.

Occasionally the gland is completely destroyed, without signs of suprarenal inadequacy. At St. Bartholomew's Hospital, during thirteen years, four examples of caseation of both suprarenals were discovered post mortem which had led to no symptoms during life. Leyton suggests that the similar cells in connection with the sympathetic chain have assumed the function of the gland.

It must be admitted that the treatment of Addison's disease by suprarenal extract has so far been very disappointing. Nothing at all comparable to the success of thyroid medication has been recorded. The best results have been in chronic cases, without additional lesions elsewhere.

The probable explanations for this lack of success are these:

1. Unlike the thyroid, which is a reservoir of the active principle, the amount of adrenalin in the gland at any moment is very small. This objection will not apply, of course, to cases where adrenalin itself is used, and not suprarenal extract.

2. It is doubtful whether adrenalin is absorbed sufficiently to be really effective when given by the mouth. We have seen that in the normal individual adrenalin causes no rise of blood-pressure when administered thus. It is true that it may produce a rise when given in Addison's disease, presumably because the vaso-constrictors of the stomach are in too atonic a state to respond. Leyton claims that this will aid in the diagnosis of Addison's disease. He gives 8 grains of suprarenal extract three times a day for three days, and if the patient has Addison's disease he expects a rise of more than 10 per cent. in the blood-pressure. This test frequently fails. In any case, as the tone of the bloodvessels returns, adrenalin must defeat itself, by causing a vaso-constriction which renders its own absorption increasingly difficult. This is probably the chief reason for the failure of the drug.

3. Repeated intravenous injections are impracticable and would not really take the place of the steady, continued secretion of small doses into the circulation, such as the normal gland accomplishes.

4. In some cases the patient is suffering from progressive tuberculous lesions, which are not checked by this treatment. It is possible that in the future paragangline, pituitrin, or the artificially synthesized sub-

stances, which are more stable, and therefore more continued in their action, may prove more successful.

The cortex differs in origin and function from the medulla. Bulloch and Sequeira pointed out the connection between premature sexual development and adenomata of the suprarenal cortex (Transactions of the Pathological Society, 1905). It is now generally agreed that the cortex yields a hormone which influences growth of the body and the development of puberty and sexual maturity, but always in the direction of virilism.

Deleterious Effects.—Like all powerful drugs, adrenalin has its dangers. We need not fear these bad results from local application or subcutaneous injection, since the vaso-constriction it produces so greatly interferes with its absorption. They have only been noted after intravenous injection.

1. *Mechanical Effects of High Blood-Pressure.*—The great pulmonary engorgement produced seriously limits the use of the drug as a cardiac stimulant in inflammatory diseases of the lung. As the brain cannot adequately protect itself against this rise of pressure by vaso-constriction, damage may be done here also. The use of adrenalin in spinal analgesia has been followed by convulsive seizures, due to petechial hæmorrhages produced in this way.

Repeated injection of adrenalin into rabbits has been thought to cause atheroma, aneurysmal dilatations, and hypertrophy of the heart. This accords with the observation that anything causing a persistently high pressure leads to arterial degeneration. But rabbits are very liable to arterial degeneration without such

injections. Philpot also noted an increase in the medulla and chromaffin material in diseases associated with high blood-pressure.

2. *Glycosuria.*—This will be discussed in the chapter on Glycosuria in general.

3. *Toxic Effects on the Tissues.*—Necrotic areas have been found in the centre of the lobules of the liver, outside which were areas of fatty degeneration. They have been attributed to the shutting off of the arterial blood by the intense vaso-constriction. I have seen similar changes in the liver of a child to whom I had given an intravenous injection of 15 minims, but the child had broncho-pneumonia, which often leads to fatty liver. In the kidney, cloudy swelling and desquamation of the tubular epithelium have been seen after injections of adrenalin both experimentally and clinically. However, Butler's case, in which as much as 88 minims were injected in all, recovered, so that if the damage be due to the drug it apparently is not permanent.

Summary.—Adrenalin, which is formed in the medulla of the suprarenal, is a benzene compound probably derived from the aromatic group in the protein molecule. It is not destroyed by simple boiling, but is rapidly destroyed by oxidizing agents, which turn it brown; apparently it is quickly dealt with thus in the tissue it excites. It loses its activity in the presence of alkalies. It is probably absorbed with great difficulty from the alimentary canal. Its application to any part produces the same effect as if the sympathetic nerves to that part had been stimulated. It may be freely applied locally, though some observers

think that caution is needed in the case of the nasal mucous membrane and (in old people) the eye. Subcutaneous injections are usually safe, though repeated injections may cause necrosis in ill-nourished parts from the local anæmia produced. Intravenous injection is the only method of producing a general, as opposed to a local effect, and this is not free from risk. The best results have been obtained in cases of bleeding from any part of the alimentary canal, but it is also useful in asthma, in vomiting, and in preventing the absorption of poisons. It is contra-indicated in hæmoptysis and in cerebral hæmorrhage. It may be used to delay the return of serous exudates, and is an adjuvant to local anæsthesia. In Addison's disease it is usually disappointing, though occasionally improvement occurs.

The Pituitary Body (Hypophysis Cerebri) and Pituitrin.

In its double origin—in part nervous, in part epithelial—this structure offers an interesting parallel to the suprarenals. The glandular lobe is larger and anterior, the nervous lobe is smaller, posterior, and connected with the floor of the third ventricle by a stalk. The glandular portion also surrounds the posterior lobe by the pars intermedia. The anterior lobe forms a colloidal secretion rather like that of the thyroid, while the posterior portion discharges a substance—*pituitrin,* somewhat resembling adrenalin in action—into the cerebro-spinal fluid by way of the third ventricle.

The secretion of the anterior lobe appears to have an

effect upon body temperature, growth, the cutaneous tissues, and the sexual organs. Thus, after removal of the gland, the temperature becomes subnormal, while the injection of its extract causes a febrile response, either when this lobe has been experimentally removed or when it is diseased. This has been used as a diagnostic method, and administration of anterior lobe extract by the mouth has been used to raise the subnormal temperature in hypopituitarism. If the anterior lobe is removed in the young animal, retrogressive changes are observed in the reproductive organs, while the thymus remains large. The secondary sexual characters fail to develop or are much delayed. Hypopituitarism coming on in the adult is characterized by amenorrhœa in the female and by impotence in the male. On the other hand, in the early active stages of acromegaly there may be undue sexual activity.

Oversecretion of this lobe is accompanied by increase in the thickness of the skin, enlargement of the glands, cutaneous hypertrichosis, and overgrowth of the skeleton, while undersecretion is accompanied by the opposite conditions.

The influence of the pars intermedia on carbohydrate metabolism is shown in the hyperglycæmia, lowered sugar tolerance, or spontaneous glycosuria of the early active stages of acromegaly, or as the result of injection of its extract. In the later stages of acromegaly, when the gland is largely destroyed, this is replaced by hypoglycæmia and a greatly raised tolerance of carbohy-

drates, so that it is impossible to produce glycosuria by giving very large amounts of sugar, such as 400 grammes. The adiposity which accompanies hypo-pituitarism is no doubt in part due to this raised tolerance for carbohydrates, which are rapidly assimilated and deposited as fat. But the sexual hypoplasia is also partly responsible for this adiposity, for it is a familiar fact that castration or spaying results in much of the energy absorbed in the elaboration of the sexual secretions being now diverted to the deposit of fat.

The secretion of the posterior lobe, pituitrin, is mainly a stimulant to plain muscle and also to the secretion of milk. It acts on plain muscle more by increasing its sensitiveness to normal stimuli than by acting as a direct stimulant. It does not usually raise blood-pressure in a normal person, but when pressure is much lowered by shock or by experimental cutting off of the vasomotor centre it has a well-marked and prolonged action. In the same way the normal heart is but little affected by pituitrin, but a failing heart is restored in tone and increased in contractile power. Its action on the plain muscle of a healthy intestine is but slight; it has, however, a markedly stimulant effect on the same muscle when it is paretic, as in post-operative conditions. Pituitrin does not cause contractions of the unimpregnated uterus, nor does it induce labour in pregnancy, but when once labour has begun and the uterine muscle

is inert it intensifies and prolongs the pains and decreases the intervals between them (Blair Bell). It dilates the pupil of an excised eye, and causes contraction of the bladder muscles.

The earlier observations on the diuretic effect of pituitrin have been shown to be due to the disturbing influence of the anæsthetic. There is now no doubt that injections of pituitrin diminish the output of urine both in the normal subject and in diabetes insipidus. I have seen the injection of 1 c.c. of pituitrin relieve the polyuria of diabetes insipidus for sixteen hours, and should regard this disease as due to defective secretion of the posterior lobe of the pituitary gland, either from nervous inhibition or structural disease of the gland or its neighbourhood, such as a syphilitic meningitis. In every case of diabetes insipidus it is therefore important to have a skiagram of the skull taken and Wassermann's reaction done.

Therefore in the early stages of acromegaly in addition to pressure symptoms on the optic nerves (such as atrophy and bitemporal hemianopsia) and on the brain (such as headache), we find high blood-pressure, lowered sugar tolerance, or spontaneous glycosuria, overgrowth of the skeleton and cutaneous structures, and pressor substances in the urine. In the later stages the blood-pressure falls, the sugar tolerance is high, but the bony changes are permanent. In primary hypopituitarism (Fröhlich's syndrome) the skin is smooth, transparent, and free from moisture, the axillary and pubic hair is scanty or absent, the nails

are small and thin, and pigmentation may be present. The blood-pressure is low, the sugar tolerance is high, there is general adiposity, and loss of sexual power. In some cases the symptoms are complicated by the fact that glandular enlargement may be parenchymatous with increased secretion or cystic with diminished secretion. Therefore pressure effects may coexist with diminished function. And when one lobe enlarges, it may first irritate and finally destroy the secretion of the other lobe. So that various permutations and combinations of symptoms may result, *e.g.*, by irritation of the posterior lobe, while there is deficiency in the normal secretion of the anterior lobe. Moreover, there may be compensatory enlargement of the thyroid. Some of these points are dealt with further in the chapter on Glycosuria.

In pregnancy there may be temporary overgrowth of the pituitary, so that the facies alters, slightly approximating about the nose and mouth to that of acromegaly, while glycosuria may occur.

Substitution therapy with pituitary extract has not been very successful. In active acromegaly it cannot be expected to do good; in pituitary deficiency large doses are recommended by Cushing, such as 12 grains of the dried whole gland three times a day, while as much as 300 grains have been given in a day.

Pituitrin, the hormone of the posterior lobe, has been used successfully for its vaso-constrictor effect in shock, particularly when due to anæsthetics, and as a stimulant in intestinal paresis. It may also be tried in

asthma, especially, as already stated, together with adrenalin. It has also been used with apparent benefit in exophthalmic goitre and intestinal hæmorrhage. Blair Bell, who made the first clinical observations on the subject, has used it for *post-partum* deficiency of uterine tone. It has been recommended as superior to ergot in this capacity, but before delivery its use is subject to the same limitations as that drug.

Hamill has shown that it can be absorbed when given by the mouth, though it is more certain in its action when given intramuscularly or intravenously. In conditions of shock the best method is to add it to an intravenous saline. The dose ranges from ½ to 1 c.c., and it can be given three or four times a day.*

Other Hormones.

Therapeutical applications of other hormones need be dealt with only briefly. Those concerned with the digestive organs are discussed in other chapters; in the remainder the active principle has not been isolated yet, and until this is done we are working in the dark.

Ovary.—Marshall and Jolly believe that the changes in the uterus which determine menstruation are due, not to ovulation, but to an internal secretion arising from the ovary, probably from its interstitial cells. Extirpation of the ovaries in early pregnancy prevents the fixation of the ovum, and Fraenkel states that the destruction of the corpora lutea by the galvano-cautery

* For further details see the admirable papers of Cushing and his colleagues.

is as efficacious as total removal of the ovaries in bringing pregnancy to an end. Now, the corpora lutea are also derived from the interstitial cells of the ovary. It would appear that these provide a secretion which is essential to the activity of the uterine mucosa.

This explains why the corpus luteum persists if pregnancy occurs, but soon atrophies if it does not.

It is possible that extracts of corpus luteum or of interstitial ovarian cells might be useful in those cases where abortion occurs repeatedly in the early months of pregnancy.

In animals where the ovaries have been removed, the phenomena of heat may be reinduced by the injection of ovarian extracts. Ovarian extract has therefore been tried for the relief of symptoms following ovariotomy or at the climacteric. On the whole it has been more successful in coping with the vasomotor disturbances than with the neurotic symptoms. Benefit has been reported from its use in the treatment of melancholia or mania associated with uterine or ovarian disease, and in exophthalmic goitre.

Wherever the efficacy of ovarian extract is being tested, it is important that the patient should be in ignorance of the nature of the drug, in order to avoid the element of suggestion.

How does the mammary gland undergo hypertrophy in pregnancy and become functionally active as soon as pregnancy terminates? No nervous connection has been made out between the uterus and these glands, so that a chemical stimulant is suggested. Starling

thought he had found this in the fœtus, but the corpus luteum is more probably the source.

Testis.—The contrast between the condition of a person in whom the testes are undescended and one from whom they have been removed has naturally led to the opinion that these structures form an internal secretion responsible for the production of the secondary male characters, which persist in the former case.

Shattock and Seligmann found that the occlusion of the vasa deferentia does not hinder the full development of these secondary characters. We must distinguish this, however, from the effect of ligaturing the whole spermatic cord, which would bring both internal and external secretions to an end. They regard the interstitial cells as the probable source of this internal secretion, and it is noteworthy that after ligature of the vas these cells remain unaltered, although the spermatogenic tissue degenerates. This is indeed the basis of Steinach's treatment; he claims that such a procedure diverts energy from the formation of an external to that of an internal secretion by the gland, with consequent enormous increase in bodily activity, amounting to rejuvenescence. These claims must be allowed time to find their level. Voronoff's grafting operation is also still on its trial, though I have seen some promising results.

Brown-Séquard believed that subcutaneous injections of testicular extract produced a rejuvenating effect on himself at the age of seventy-two. Here the element of auto-suggestion certainly played a part.

Perhaps because of the exaggerated claims made for it, this treatment fell into discredit, which reacted unfavourably on organo-therapy as a whole.

Poehl attempted to place it on a more scientific basis; he prepared from the gland a crystalline substance—spermin—which he regarded as a catalytic agent, increasing oxidation, and thus acting as a powerful physiological tonic. But Loewy and Richter did not find that it altered the oxygen exchange of castrated animals.

Many of the preparations of testicular substance used are rich in organic phosphorus and lecithin. When these factors, as well as that of suggestion, are excluded, the evidence as to the benefits claimed for them in nervous diseases, psychoses, impotence, and a host of other conditions, shrinks to slender proportions.

Thymus.—The thymus is an infantile organ that tends to disappear spontaneously, and whereas there is an association between the cortex of the suprarenal and sexual development, there appears to be an equally definite antagonism between the thymus and the sexual organs. Thus Henderson found that castration in young cattle delayed the normal atrophy of the thymus, while Paton and Goodall have shown that excision of the thymus in young guinea-pigs was followed by rapid growth of the reproductive organs. No other changes were noted beyond a diminution of the leucocytes, affecting all tho varieties, which lasted for two months. The gland is a special infantile organ

for forming white corpuscles, which are more numerous in the circulation of the child during the normal period of activity of the thymus. As nucleated red cells have been found in the gland, it is possible that it may form erythrocytes also. No active extract has been prepared from the organ, so there is no evidence that it forms an internal secretion, nor do thymus extracts appear effective in disease.

The enlargement of the thymus in cases of Graves' disease is interesting, in view of the development of both thyroid and thymus from branchial clefts. In one fatal case I found Hassall's corpuscles (usually regarded as remains of the epithelium of the gill-slits) enormously hypertrophied. As Graves' disease does not occur till after the thymus should have disappeared, its persistence in this disease raises the interesting suggestion that only those who are the subjects of persistent thymus can suffer from Graves' disease.

The association of enlargement of the thymus with sudden death is, strictly speaking, outside our present subject. The enlargement is usually merely the most striking example of a general lymphatic overgrowth, to which the name of 'lymphatism,' or status lymphaticus, has been given. The condition is commonest in infants, though not unknown in adolescents. The subjects are usually plump and flabby, with a pasty complexion. Hypertrophy of the tonsils, perhaps a slight swelling of the thyroid, and sometimes dulness behind the sternum, may be detected.

Death may be dramatically sudden, or there may be

'thymic asthma,' followed by heart failure. They succumb readily to anæsthetics; chloroform and ether seem equally dangerous. After a brief administration the patient may go rigid, or have a slight tetanic convulsion, and die forthwith. It is possible that some of the cases of sudden death while bathing are due to lymphatism. There is no doubt that lymphatism is a real condition; the pardonable scepticism which exists as to its reality is due to its being invoked to explain too many misadventures.

Four explanations have been given of the sudden death:

1. *Pressure* on the trachea, the vagus, or its branches. Flattening of the trachea has been observed post mortem, and relief of dyspnœa has followed raising of the gland from the trachea by operation. Thymic death is not from asphyxia, however, but from syncope.

Nor could death be due to laryngeal spasm from pressure on the recurrent laryngeal nerves. Such spasm to be fatal must be bilateral, and the right recurrent laryngeal nerve hardly enters the thorax at all. Moreover, there is not the typical crowing inspiration of laryngeal obstruction.

Pressure on the vagus is possible, and would cause syncope.

2. *Intravascular clotting.* An extract of thymus gland will cause intravascular clotting, and therefore sudden death, but this does not represent a normal internal secretion of the thymus, and simply owes its activity to the thrombokinase it contains. More-

over, intravascular clotting is conspicuously absent in cases of 'thymic death.'

3. *Toxæmia.* The general hypertrophy of the lymphoid tissue suggests that the body is reacting to some infective process. The adenoid tissue of children has a great tendency to react to irritation. On this view the death is merely the terminal event of a prolonged intoxication, the nature of which is at present unknown. The toxin is presumed to act on the respiratory and cardiac centres in the medulla.

4. *Anaphylaxis.* The sufferer from status lymphaticus is prone to anaphylactic shock which may be fatal.

Kidney.—There is no evidence of an internal secretion formed by the kidney. Rose Bradford observed increased excretion of urea after removal of a considerable proportion of the substance of the kidneys in dogs, which was thought to point to a regulation of nitrogenous metabolism by an internal secretion. Beddard and Bainbridge have shown that this rise in nitrogenous output was probably merely that of the later stages of starvation from any cause. Extracts of kidney have not met with any therapeutical success.

Muscle.—The use of meat-juice (zomo-therapy) in pulmonary tuberculosis, and of meat-extracts to stimulate secretion of acid in the gastric juice, may also be classed as examples of organo-therapy.

Though many other organic extracts have been used empirically, it cannot be said that they

have achieved, or, for that matter, have deserved, much success; for the preliminary proof that the extracts contained any active principle whatever has been lacking. Starling looks forward to an important future for organo-therapy conducted on right lines when he says: 'If the mutual control . . . of the body be largely determined by the production of definite chemical substances in the blood, the discovery of the nature of these substances will enable us to interpose at any desired phase in these functions, and so to acquire an absolute control over the working of the human body. Such a control is the goal of medical science.'

Far though we may be from such a goal, the study of hormones offers a profitable field for research. For it is only by an exact knowledge of the bodily processes in health that we can learn to intervene effectively in disease.

CHAPTER II

THE RATIONAL TREATMENT OF GASTRIC DISORDERS

Recent important additions to our knowledge of the digestive processes have modified the rational treatment of gastric disorders.

The Nervous Factor in Gastric Digestion. — We owe the fundamental experiments on this subject to the Russian school of physiologists. Pavloff, by dividing the œsophagus in dogs, and fixing the divided ends to the skin, completely separated the cavities of the mouth and stomach. Food taken into the mouth would naturally drop out of the gullet: this is termed 'sham feeding,' but 'direct feeding' could also be carried out by passing food into the stomach by way of the lower segment of the œsophagus. In some cases a separate cul-de-sac was made out of a portion of the stomach. This pocket opened on to the surface, so that the digestive processes in it could be easily observed; it was found that they were an exact reflection of those occurring in the main stomach.

He found that in such a dog the taking of food by the mouth was followed after an interval of five minutes by a copious secretion of gastric juice; in fact, it was

not necessary for the food even to be swallowed. If the dog were shown the food, secretion would follow, until the animal realized it was not going to get it.

Clearly, a nervous agency must be at work. Now, if one vagus were previously divided below the recurrent laryngeal and cardiac branches, and the other drawn into the wound, the latter could easily be cut while the animal was feeding. It was found that now 'sham feeding' produced no effect. Conversely, if the vagus had been previously drawn into the wound and divided, to allow the cardio-inhibitory fibres to degenerate, stimulation of the peripheral end, too weak to cause the animal any pain, led to a secretion of gastric juice.

On the other hand, 'direct feeding' into the stomach led to hardly any secretion, if the animal did not see the food.

The value of an appetite in aiding digestion was more clearly proved by the following experiment: Two dogs had 100 grammes of meat introduced direct into the gastric cul-de-sac; one dog's attention was distracted, so that he did not know he had received food, while with the other a vigorous 'sham feeding' was kept up at the same time. In the first hour the first dog digested only 6 grammes, while the other digested 30. The difference represents the digestive value of the passage of food through the mouth, and the consequent rousing of the appetite.

The character of the juice poured out varied greatly with the diet that excited it. Thus, a meal of bread

caused the secretion of a small amount of juice, rich in pepsin, but poor in acid. Meat caused a much larger secretion of a juice weaker in peptic power, but containing more acid. Milk required even less pepsin to digest it than meat. Bennett and Dodds, however, consider that in modern man whose stomach is frequently filled before ever appetite has had an opportunity to become awakened, the psychic factor is not of great importance.

The Chemical Factor in Gastric Digestion.—Mechanical stimulation of the gastric mucosa will lead merely to an outpouring of alkaline mucus, but certain chemical stimuli will result in true secretion. As clinically chemical factors are more under our control than nervous ones, these are of practical importance.

We may arrange the effect of articles of diet as follows:

1. Substances producing a powerful secretion: Meat extractives such as are contained in soups, broths, and beef-tea. The secretion begins in thirteen minutes. Bickel found that in human beings alcoholic and carbonated fluids, spices, mustard, pepper, salt, cloves, also produced an abundant secretion. Craven Moore and Allanson found that tea was a stimulant to secretion, and coffee still more so in some individuals, though variable in its action. A cigar after meals stimulates secretion in an habitual smoker.

2. Substances producing a slight secretion: Milk, gelatine, water.

3. Substances producing no secretion: Egg-white, proteose, peptone, starch, sugar, salts of meat.

4. Substances inhibiting secretion: Fats and sodium bicarbonate.

In fact, secretion occurs in two stages, the first depending on the stimulation of the sense of taste while the food is yet in the mouth, the second occurring when absorption has begun. The mechanism of this second secretion has been shown by Edkins to depend on a chemical factor, which explains the occurrence of digestion after division of the vagi. The pyloric glands differ widely in structure from the glands in the fundus of the stomach. Though the latter are simple tubular glands, they are composed of highly differentiated cells, the granular chief cells secreting the pepsin and rennin, the ovoid parietal cells forming the hydrochloric acid. Passing to the pylorus, we find a marked change in the plan of the glands, which have become wide-mouthed and branched; the lining cells are neither granular nor ovoid, but closely resemble those covering the surface of the stomach.

No theory of gastric secretion can be satisfactory that does not account for these striking differences of structure. It is the merit of Edkins' work that it at once explains the structural difference and the method of secretion in the absence of nervous impulses. He found that an extract of pyloric mucous membrane injected into the circulation of a fasting animal would cause the secretion of a juice containing both hydrochloric acid and pepsin. A similar extract of fundus glands produced no effect. Pyloric glands, therefore, produced a chemical stimulant or hormone to the con-

tinued secretion of gastric juice by the fundus glands, which is termed *gastric secretin.*

He tested the efficacy of certain substances in evoking this stimulant in the pyloric glands. Meat-extract was the most marked and consistent in its effect, the percentage of acid being from 0·05 to 0·16 per cent. After meat-extract came dextrose and then dextrin. Hydrochloric acid itself had very little effect.

He then divided the stomach into two portions by a tampon, and was able to prove that all the active juice was formed in the fundus, while the function of the pyloric portion was absorptive.

It follows that, as the food passes over into the pyloric portion, it can be sent on into the duodenum, if it be already sufficiently digested, but otherwise it is kept in contact with the pyloric glands, where it evokes renewed secretion from the fundus glands to complete its digestion. And, indeed, if the appetite and sense of taste were the only stimulants to secretion, how would digestion be completed when the former was assuaged and the latter no longer exercised? Many animals, their hunger being satisfied, soon fall asleep. We see now that the secretion, started by nervous impulses, is continued by chemical stimuli, which will act as long as there is food in the stomach.

Movements of the Stomach.—This is a subject on which X rays have given us much information in recent years. The œsophagus enters a little below the highest point, the part above the œsophageal opening being always occupied by a certain amount of

gas. Then comes the body of the stomach, mainly vertical, and separated from the pyloric portion by the incisura angularis. The greater curvature reaches 1½ inches below the umbilicus. As shown by Hurst, there is a great difference between the appearance of the stomach with the X rays and its position as determined by any method of percussion.

The amount of bismuth which is given for the purpose of taking X-ray photographs is 4 to 6 ounces of the carbonate or the oxy-chloride. These do not produce toxic effects, although the subnitrate may. Barium sulphate is also used, as it is cheaper, but it gives a less definite shadow. Either is given with ground rice, gruel, bread and milk, or suspended in water, with some lactose. A thin emulsion is now frequently used, which can by manipulation be pressed into different parts of the stomach. It is, of course, necessary, before examining a patient in this way, that he should not have bismuth as a medicine for two or three days beforehand, otherwise the shadow will be obscured. The stomach should be examined both in the erect and in the recumbent postures, and omission of this precaution has led to serious errors. In the recumbent posture the stomach normally tends to adopt an hour-glass shape, from the weight of the bismuth on either side of the vertebral column.

Although the mere weight of the meal must affect the appearance of the stomach, this does not interfere with comparisons between the healthy and the diseased organ. The stomach may change its shape within wide limits and yet be perfectly normal. As Sherring-

ton puts it, there is a variation in its *posture* by which the effect of gravity is overcome. Such changes are merely variations in the degree of tone. For this the circular and longitudinal muscular coats are responsible. They also produce the peristaltic waves, but the two functions appear to be independent of one another. The oblique band of muscles acts as a sling supporting the stomach. Fluid passes down the empty stomach in any of the channels formed by the rugæ, especially in those close to the lesser curvature. Solids are held up for a time at the cardiac end. In general terms, the cardiac end is a reservoir, the pyloric antrum a mill (Sherrington). Peristaltic waves are, therefore, much more active at the pyloric end, and can be seen sweeping towards the sphincter about three times a minute, gaining force as they go. As the stomach empties it is pulled up until the pyloric orifice becomes the lowest part, which assists the completion of the process.

Cannon found that if carbohydrate be taken at the beginning of a meal it soon passes into the duodenum, but if protein be taken first the onward passage is delayed. This is because the acid of the gastric juice does not become fixed by carbohydrate, but, remaining free, is able to influence the sphincter; protein, on the other hand, fixes the acid so that until digestion has proceeded far enough to set the acid free again the pylorus remains closed.

This is an adaptation to the fact that carbohydrate cannot be digested by gastric juice, so that as soon as acidity has put an end to salivary digestion no useful purpose is served by its retention in the stomach.

Whereas acid on the gastric side of the pylorus tends to open the sphincter, as soon as it reaches the duodenum it leads to closure of the orifice. This, as Cannon points out, is in accordance with the general law of peristalsis, that dilatation occurs below and contraction above the place of stimulation. Long after the fundus has returned to its fasting condition, the pyloric portion contains food, and shows those vigorous waves of contraction which form the 'gastric mill.' The semi-digested food is thus kept in close contact with the glands in which the stimulant to gastric secretion is elaborated, thereby providing for its own digestion. The much greater frequency of lesions at the pyloric as compared with the cardiac end is probably due to injuries incidental to its greater activity.

Practical Deductions.

The nervous factor in gastric digestion affords a scientific explanation of the old adage, 'Hunger is the best sauce.' Indeed, as we have seen, it is a sauce which will increase the rate of digestion fivefold. This should lead us to attach great importance to the personal equation in dieting a patient. Too rigid a dietary, albeit compiled on an admirable chemical basis, may prove distasteful and upset the appetite, thereby preventing all the good that might be expected. Nevertheless, in neurotic patients the very rigidity may cause interest, and thus excite the appe-

tite. I once saw an example of this in a typical neurasthenic. He complained that his food 'did him no good,' and he lost flesh until, becoming alarmed, he underwent a 'cure' in Germany. It depended on an exact analysis of all the excreta, on the result of which the menu for the next day was drawn up. This process, which would have been repulsive to the average man, excited his interest keenly, and he throve greatly. He is now firmly convinced of the unscientific character of English physicians. The personal equation is, I think, too often neglected. Thus, fat has an inhibitory effect on gastric secretion in any case; to force it on a child who loathes it may be good moral discipline, but it is certainly bad physiology.

Our dietetie restrictions and prescriptions are too much dictated by fashion. Except in cases where we must forbid something for a perfectly definite reason, our patient's likes and dislikes should be carefully considered; whereas it is our own likes and dislikes which reappear constantly in our dietetic schemes. Given a certain knowledge of the man, one can predict fairly accurately what he will recommend to any patient. The dyspeptic is often a diligent seeker after medical advice, and when he tries to harmonize the various dietetic gospels he has received, his opinion of our profession is not enhanced.

'There is to be observed a sort of fashion running through these restrictions,' says Sir William Roberts, 'yet I know not on whose authority they repose. . . . They are, for the most part, quite unmeaning; they

stand on no ground of science or experience, and are gratuitously punitive to our patients. . . . There are cases in which a certain amount of coercion is salutary and even necessary. In neurotic and hysterical persons the stomach sometimes shares in the general instability, or it may even be the chief offender.'

It is curious that often quite opposite methods of restriction should both be successful. A patient goes to one physician, whose opinion is that all purins are deadly poisons. He is put on a purin-free diet, and improves. Tiring of the restrictions, he seeks advice from another physician, whose opinion is that most ills are due to incomplete combustion of carbonaceous foods. These are now restricted, while he takes meat freely, and again he improves.

The explanation is that this is a type of patient who eats and drinks too much. Variety of diet stimulates his appetite, while the monotony entailed by abstention from so many pleasant things results in his eating less altogether.

In fact, there are surprisingly few instances in which the addition of or abstention from some particular article of diet can be relied upon to produce a specific effect. Examples will be considered in their appropriate places.

The late Sir Andrew Clark was accustomed to forbid his dyspeptic patients to take soup, on the ground that, by diluting the gastric juice, it prevented diges-

tion from proceeding. The advice was good in many cases, though the explanation was unphysiological. At this stage the gastric juice has not been secreted, and therefore cannot be diluted. Moreover, of all the chemical excitants of gastric secretion, meat-extracts have proved the most efficacious. To a tired man the warm fluid, causing gastric vaso-dilatation, and containing a stimulant of the gastric juice, while not in itself taxing the digestive organs, is an excellent beginning to a meal. It is important to note that meat-extracts mainly affect the production of hydrochloric acid, and cause little secretion of pepsin. In hyperchlorhydria, therefore, meat-soups are distinctly contra-indicated, while to dyspeptics with inadequate gastric secretion they are beneficial.

This explains the discrepancy between the results of analysis of meat-extracts and the popular estimate of their value. Their nutritional worth, so far from being accurately represented by pictorial advertisements, is stated to be equivalent to that of a teaspoonful of milk in a tumblerful of water. Yet as stimulants of gastric juice they have a decided place, and a patient may be able by their aid to tolerate a restricted and uninteresting dietary. But we must remember that we are not giving food; we are only preparing the way for food.

The tax which vegetable as compared with animal protein imposes upon pepsin should not be forgotten in the construction of a dietary. Herein lies the

advantage of lightly cooked minced meat; it requires little pepsin, it does not easily ferment, and it does not leave a large indigestible residue. It is for this reason that it has proved useful in dilatation of the stomach. Surely it is a fallacy to administer so much starchy food in dyspepsia, as is frequently done, when we consider its liability to ferment and the quantity of juice required for its digestion. A preparation that looks like milk does not necessarily become digested like milk! Harry Campbell has protested strongly against starchy food in the form of pap. It has to be swallowed at once, without any chance of salivary digestion, while in the solid form, requiring a good deal of mastication, it excites enough secretion of saliva to initiate its conversion into sugar. For this reason toast, biscuit, and rusk can often be digested when new bread or mashed potatoes cannot.

In many respects the physiologist's discoveries have been anticipated by the chef. We see the advantage of beginning a meal with soup to excite secretion, and of finishing with sweets, when the cardiac portion of the stomach will retain the food and permit continued digestion of the carbohydrates by the saliva. The postprandial cup of black coffee receives scientific sanction. The surroundings of a meal may have a physiological as well as an æsthetic value.

Pavloff's experiments also explain the different value attached to bitters by the clinician and the pharmacologist. It is true that, introduced directly

into the stomach or into the circulation, bitters are ineffective, but by exciting the nerves of taste and arousing the appetite while passing through the mouth they may be a distinct aid.

This has an important application in the treatment of patients on whom gastrostomy has been performed for stricture of the œsophagus. That the stricture is usually malignant is held to be sufficient explanation of the fact that such patients do not thrive. But they are also losing the powerful aid of 'appetite juice,' since the food no longer passes through the mouth. It is easy and rational to place sapid substances in the mouth to excite the sense of taste, while feeding through the gastrostomy wound is going on.

I know of one case in which the patient himself requested that he might take the food into his mouth and, after mastication, place it in his stomach through the gastrostomy wound. The request was granted, and the change seemed to benefit him. It was considered merely an unpleasant eccentricity on his part, whereas really he had anticipated Pavloff's discovery.

The Acid of the Gastric Juice.

Of all the constituents of gastric juice, hydrochloric acid is the most variable. Pepsin disappears in achylia gastrica, and is much diminished in gastric carcinoma, but otherwise alters but little in disease. How important the hydrochloric acid is can be realised by enumerating its functions.

1. It is essential to the activity of pepsin, which is powerless in a neutral medium.

2. It is antiseptic.

3. It hydrolyzes starch to some extent, like any other mineral acid.

4. It regulates the pyloric sphincter.

5. It is a stimulant to the pancreatic secretion.

In gastric disorders it is often the hydrochloric acid that holds the key to the situation. If there were no hydrochloric acid, one would expect no digestion in the stomach, while fermentation would proceed apace in the absence of the normal antiseptic.

The method of fractional test meals has, however, shown that even in healthy individuals there is a considerable variation in the secretion of hydrochloric acid. The fasting contents of the stomach are removed before a meal of oatmeal gruel is given. An Einhorn tube is passed and small quantities of the gastric contents are removed at regular intervals by suction for analysis. The total amount should as a rule be withdrawn at the end of 2½ hours.

Bennett and Ryle used this method on 100 healthy medical students and plotted out the curves obtained. Of these 91 showed an iso-secretory curve—that is to say, that in spite of individual variations the percentage of free HCl rose steadily during the first hour and subsequently fell towards its original concentration. Four of these 91, however, showed a much shorter curve of a similar type, the stomach being empty in three-quarters of an hour. Of the remaining

nine, four showed a complete achlorhydria, although they had no dyspeptic symptoms and they remained quite well for the two years they were under observation; five showed a climbing type of curve, such as is associated with juxta-pyloric ulcers and pylorospasm. It is important to note that this method gives the *concentration* of the acid secreted, which is a very different thing from actual *amounts*.

Dodds has confirmed these observations by a different method. He has shown that during the secretion of the hydrochloric acid into the stomach, there is a rise of CO_2 in the alveoli of the lungs, and a fall during the secretion of pancreatic juice. His explanation is that the secretion of acid into the stomach would tend to lower the hydrogen-ion concentration of the blood, if this were not prevented by the blood retaining CO_2, with consequent diminution of pulmonary ventilation, so that the CO_2 in the lungs is not washed out so much. On the other hand, the secretion of alkaline pancreatic juice from the blood would raise its hydrogen-ion concentration if there were not increased pulmonary ventilation to wash out CO_2 as well. This rise and subsequent fall correspond accurately to Bennett's and Ryle's results and further serve to distinguish between the secretion of a little acid of higher concentration and of a larger amount of acid, although of lower concentration. For in the latter instance the rise of alveolar CO_2 will be greater.

It is too early as yet to come to final conclusions on these observations. It must be admitted, however,

that they seem to make the acid of the gastric juice of less importance than has hitherto been believed, for, as Bennett says, in healthy young adults achylia gastrica appears to be about as common as red hair. The authors lean towards a local nervous reflex as the important factor in gastric and pancreatic secretion, since they find that the local application of atropin to the gastric or pancreatic mucosa prevents this rise and fall respectively.

The principal conditions under which the acid of the gastric juice is deficient or absent are :

1. Chronic gastritis.

(*a*) Simple atonic, in which only the hydrochloric acid is reduced.

(*b*) Mucous, in which the acid is reduced, while the mucus is considerably increased.

(*c*) Atrophic (achylia gastrica), in which hydrochloric acid, pepsin, and rennin are all absent. This may also occur in pernicious anæmia.

(*d*) The gastritis of cirrhosis of the liver.

(*e*) The gastritis of congenital hypertrophic stenosis of the pylorus in infants.

2. Malignant disease.

Hydrochloric acid is usually absent from the gastric juice in malignant disease of the stomach, and always reduced. Various explanations have been given for this.

(i.) Reissner found that, although there was loss of free hydrochloric acid in the gastric juice, the total chlorides were not decreased. This points to the

neutralization by alkaline fluid secreted by the surface of a new growth. Graham's observations on the increased ratio of mineral chlorides to active hydrochloric acid confirm this.

(ii.) B. Moore and his colleagues maintained that there is a low secretion of free hydrochloric acid when malignant disease is present anywhere in the body, and not simply in the stomach, due to a diminution of hydrogen ions in the blood. While it seems clear that if metabolism be sufficiently depressed the output of acid is decidedly affected, it is too much to claim that malignant disease is peculiar in this respect. While hydrochloric acid may be absent in any cachectic condition, the active acid is not necessarily diminished in early or uncomplicated carcinoma of organs other than the stomach. Copeman and Hake found that in mice with carcinoma of other organs than the stomach there was no reduction in the active hydrochloric acid, but even a slight increase. And, as Willcox points out, it is illogical to draw a distinction between free HCl and HCl combined with protein.

(iii.) Another factor that seems to me to have been overlooked is the loss of gastric secretin, which is a powerful stimulant to the secretion of the acid. The pyloric region is the one most frequently affected by cancer, and though hydrochloric acid is not formed there, destruction of the pyloric glands involves the loss of the chemical factor in gastric secretion. This would explain the cases where the total secretion of chlorides is low.

With all these influences—neutralization, depressed metabolism, and loss of the chemical stimulant—at work, the absence of free hydrochloric acid is not surprising.

The principal conditions under which the acid of the gastric juice is increased are:

1. 'Sthenic' dyspepsia, or the so-called acid dyspepsia of otherwise healthy persons.
2. Peptic ulcer, gastric or duodenal.
3. Chlorosis.
4. Cholelithiasis.
5. Chronic appendicitis.
6. Colitis.

Craven Moore suggests the term 'reflex dyspepsia' for hyperchlorhydria, which has the advantage of emphasizing the method of its production. It implies the existence of a lesion or an increased excitability of the reflex nervous mechanism, often both. If the lesion is severe, it can make itself felt, even though the nervous system is normal; but if the nervous system is unduly irritable, a very small lesion may produce marked symptoms. Thus we can understand why it occurs in the type of man it does, and why the man 'who in the prime of manhood was a martyr to dyspepsia . . . in his later years, when his nerves are blunted . . . eats and drinks with the courage and success of a boy.' Another factor in the production of hyperchlorhydria which I have noted is the stimulus of a change of diet, such as occurs during a Continental holiday.

I do not think we can go as far as Moynihan in asserting that all cases of hyperchlorhydria depend on

an organic lesion, usually an ulcer; but the diagnosis of simple hyperchlorhydria, or 'sthenic dyspepsia,' ought not to be made until every effort has been made to exclude the other conditions in which hyperchlorhydria occurs. It will be noted that these are chiefly conditions lower down in the alimentary canal. Now, if the intestine be wounded experimentally, there is inhibition of movements for some distance above, and there may also be spasm of the pylorus lasting for several hours. In the same way a duodenal ulcer, gall-stones, old appendicitis, and colitis set up a protective spasm above. This is usually at the pylorus, preventing the escape of acid from the stomach, and the regurgitation of alkaline fluid from the duodenum into the stomach. This would check neutralization and therefore give a higher yield of acid in the test meal (Bolton and Goodhart). Hyperchlorhydria then does not necessarily mean increased secretion. The contraction of the stomach against a closed pylorus would increase intragastric tension which would explain the occurrence of pain. The existence of this spasm is readily demonstrated by the X rays. The leading symptoms in hyperchlorhydria are:

1. **Pain**, especially towards the end of digestion, when the stomach is getting empty. The pain, therefore, comes on sooner after a light meal, such as afternoon tea, than after a heavy meal. Thus, after evening dinner there may be freedom from pain till the middle of the night. The taking of food temporarily relieves the pain. This characteristic symptom

of hyperchlorhydria has been called 'hunger pain' by Moynihan, who regards it as pathognomonic of duodenal ulcer. This pain is not the direct effect of hyperacidity, for Hurst has introduced stronger acids than are ever found in hyperchlorhydria without evoking it.

Moreover, in duodenal ulcer the stomach begins to empty quickly, and although during that time acid contents are passing over the ulcerated surface there is no pain; but later on when, as X rays show, the pylorus has gone into spasm, the pain returns.

2. **Pyrosis.**—This term should be kept, as Sir William Roberts advised, to a paroxysm of gastric cramp, accompanied by a sudden gush of saliva into the mouth. It is an attempt on the part of the body to neutralize the excessive acidity of the gastric juice by the alkaline saliva, but, like so many pathological attempts at repair, it overshoots the mark; for it is impossible for such a quantity of saliva to be swallowed. Cardiospasm may increase this symptom by preventing the saliva from entering the stomach.

3. **Appetite for Indigestible Things.**—The patient feels more comfortable when the gastric juice is given plenty to do, and therefore he often eats largely. There may be a positive craving for fat, which is comprehensible in view of its inhibitory effect on gastric secretion.

Much can be learned from a careful comparison of the symptoms of hyperchlorhydria and achlorhydria, and I have placed the most important points of contrast in parallel columns. For many of these I am indebted to the writings of Leonard Williams.

	Atonic Dyspepsia.	Reflex Dyspepsia.
Test meal	Diminished HCl	Increased HCl.
Type of patient	Weakly, nervous, or convalescent. Generally tea-drinkers	Strong, active, energetic. Seldom teetotalers.
Mental State	Depression	Irritability.
Appetite	Capricious or absent	Voracious, especially for indigestible things.
Pulse	Quick and feeble	Good volume.
Character of pain	Discomfort usually present, becoming acute pain soon after taking food	Pain relieved by taking food, returning as the stomach is getting empty.

The occurrence of ulceration in the stomach confuses the clinical picture, since, although associated with hyperchlorhydria, it may occur in weakly, anæmic girls, and the pain, far from being relieved by taking food, is rendered acute. The localized character of the pain and the superficial tenderness will be important guides.

There are many cases, however, in which simple considerations are not sufficient, and recourse must be had to other methods of examination, such as the test meal and the X rays. Even from the test meal it would not be possible to diagnose between duodenal ulcer and simple hyperchlorhydria, but in the examination of the fæces for occult blood we have a very important guide. This is a simple enough test, and it is also valuable in the diagnosis of malignant disease of the alimentary tract, because by this method blood will be found in practically every specimen of the fæces. Small continuous losses of blood are typical of carci-

noma of the alimentary tract. In simple ulcer intermittent and larger losses of blood are more likely to be met with. If a patient has never had melæna or bright blood in the stools, but gives on three separate occasions a positive result with the test for occult blood, there is probably malignant disease of the alimentary tract.

The test is performed as follows:

Take a small portion of fæces in a test-tube, add about 5 c.c. of water and boil thoroughly to destroy any vegetable oxidases, which would give a positive result, even in the absence of blood. A little benzidene is now added to some glacial acetic acid until a saturated solution is prepared. Ten drops of this are mixed with about 3 drops of boiled fæcal extract. and then 20 drops of a 3 per cent. solution of hydrogen peroxide are added. If any blood is present in the fæces, a blue colour will appear in about two minutes. A pale green colour is not enough; it must be a real blue. Boas' reagent is less sensitive but less liable to error. It is phenolphthaleïn reduced by zinc dust in the presence of caustic soda. One c.c. of this with equal quantities of boiled fæcal extract and hydrogen peroxide, turns red in the presence of blood. These are useful additions to the methods of examination of gastric diseases. But it is very important before employing such tests that the patient should be put on a meat-free diet for three days, and that the bowels should be opened in between. A soap-and-water enema should not be used for this purpose, as soap tends to prevent the reaction. There is no objection to a simple water enema.

Principles of Treatment in Asthenic Dyspepsia (Achlorhydria).

It goes without saying that in all forms of gastric affections the condition of the teeth and gums calls for attention. Carious teeth and pyorrhœa mean that mastication cannot be duly performed, and that septic absorption is taking place. But they are specially injurious in achlorhydria, where the antiseptic action of the hydrochloric acid is lost. The improvement in gastritis after removal of this source of infection is often surprisingly rapid.

Bunge has directed some pertinent criticisms against the indiscriminate use of alkalies in fermentative dyspepsia. While it is quite true that an alkali, by neutralizing the acids of fermentation, will relieve the symptoms, it will also neutralize the hydrochloric acid of the gastric juice, without which pepsin is powerless. As this acid is also antiseptic, fermentation will proceed apace in its absence, while digestion is arrested.

Except as a palliative, the usefulness of alkalies in conditions associated with diminished hydrochloric acid is limited to their administration before meals.

Even then it is not obvious how alkalies act beneficially, though the fact is undoubted. It used to be stated that they stimulated the flow of gastric juice, but Pavloff found that they inhibited the flow of both gastric and pancreatic juices. He believes that they insure physiological rest to a stomach which is in a condition of irritable weakness. Whether this ex-

planation be correct or not, the solvent action of alkalies on mucin must surely be a help to a stomach hampered by catarrhal exudation, enabling digestion to start with a clean slate. According to Izod Bennett bicarbonate of soda also excites a subsequent secretion of hydrochloric acid in man, while magnesia does not.

While too much reliance has perhaps been placed on alkalies, certainly the use of acids has been somewhat neglected. We know that not only is the hydrochloric acid essential to the activity of pepsin and to the secretion of pancreatic juice, but that it is a valuable antiseptic, and helps the hydrolysis of the fermentable carbohydrates. We know also that its secretion fails in gastritis long before the pepsin disappears. Yet we still see dyspeptics sprinkling pepsin powders over their food while spurning the aid of hydrochloric acid.

The combined use of alkalies before meals, followed after meals by a good dose of dilute hydrochloric or nitro-hydrochloric acid with nux vomica, has given me more satisfactory results than either separately. And we should not be niggardly; for even the full pharmacopœial dose of 20 minims would only confer an acidity of 0·02 per cent. on a pint of fluid. Acidol, otherwise known as oxyntin (betain chloride) has the advantage of gradually giving off hydrochloric acid in aqueous solutions, and is more effective than the simple acid. It is quite stable in the dry state, and is readily soluble in water. Pastilles containing 7½ and 15 grains are put up, and are equivalent to about 5 and 8 minims

of hydrochloric acid respectively. They should be given freshly dissolved, and not swallowed in the solid form. Patients may tolerate the acid in this form without difficulty. But it must be admitted that it is far more difficult to rectify a deficient than an excessive secretion of acid in the gastric juice. This is probably related to some aspect of the alkali reserve of the body which is at present not understood.

In order to obtain appetite juice the idiosyncrasies of the patient must be studied. The condition is commonest in women, who are notoriously indifferent to the pleasures of the table, but whose æsthetic sense is responsive to pleasant surroundings and dainty service.

I have often allowed some food for which the patient had a special liking, even though it may have a bad reputation in dyspepsia. And the result seems to have justified this course. Articles which obviously disagree will naturally be prohibited, and it will usually be found that fats or meat with much fat in the fibre cannot be tolerated, because of their inhibitory effect on gastric secretion. As already explained, carbohydrates in the form of pap should be avoided.

Pavloff showed that he could retard the digestion of protein in dogs by mixing it with starch. And Cannon's observations suggest another important reason against this procedure if gastric secretion be inadequate. When carbohydrates are given with protein they are retained in the stomach, and can ferment. But given by themselves they pass on more rapidly

into the sphere of influence of the pancreas, where they are digested by the amylopsin. Therefore is it advisable not to give carbohydrate and protein together, but to give them as separate meals. Protein can often be tolerated as lightly cooked minced meat.

Both in this and in the opposite condition of hyperchlorhydria it will, of course, be necessary to see that the bowels are freely opened. Small divided doses of calomel, followed by a saline purge, form an important preliminary to the treatment.

The golden rules, then, which I believe should guide the treatment of atonic dyspepsia are—

1. Satisfy yourself that the case is one with diminished secretion of hydrochloric acid; in other words, make a correct diagnosis.

2. Encourage the secretion of 'appetite juice' by careful consideration of the patient's idiosyncrasies.

3. Encourage the chemical stimulation of gastric juice by a small amount of meat-extracts or beef-tea at the beginning of a meal.

4. Never give carbohydrate in the form of pap, but in a form requiring mastication, and only give very small amounts with any protein meal.

5. Avoid fats.

6. Give acidol after food, and give alkalies with bitters only before meals when catarrhal signs are present.

7. Attend to the teeth and bowels.

8. Look for early signs of dilatation and treat it by lavage.

Principles of Treatment in Reflex Dyspepsia (Hyperchlorhydria).

The cause of the hyperchlorhydria must be sought for and treated. The administration of alkalies after meals is a rational procedure for the relief of symptoms, and no doubt the success of this treatment, indiscriminately employed as it often is, is due to the large proportion of hyperchlorhydrics among dyspeptics. The best alkali for the purpose will be one that is insoluble, thus having a slow, continued action, and does not distend the stomach by the evolution of carbonic acid gas on neutralization. It is, moreover, possible that the evolution of this gas stimulates the secretion of hydrochloric acid. Accordingly, I prescribe 1 to 2 drachms of liq. bismuthi hydratis (Parke Davis), with 10 grains of heavy magnesia or 1 to 2 drachms of cream of magnesia. The combination has the advantage that, while bismuth is constipating, magnesia is relaxing. Moreover, magnesia is the most effective antacid we have. I sometimes prescribe the two drugs in separate bottles with some hydrocyanic acid and cardamoms, telling the patient to regulate the dose of each according as he is constipated or relaxed. The bismuth lozenge of the British Pharmacopœia, as recommended by Sir W. Roberts, or the magnesia lozenge called alkagen, is often effective. They should be sucked slowly, thus providing for the swallowing of much alkaline saliva as well as the alkaline drugs. Their portability is another factor in their usefulness to sufferers, who are often of an active temperament.

The addition of tincture of belladonna to a mixture may have a good effect, because it is a powerful inhibitor of secretion. Craven Moore advises the use of bromide at the beginning of treatment to depress the excitability of the nervous reflex, and I have found this a most useful addition. Kaufmann believes that lack of the gastric mucus, which is normally a protection to the stomach, is a factor in producing pain. It is probable that any success attending the empirical use of silver nitrate is due to the gastric catarrh that it induces. He advises lavage with silver nitrate solution, 1 in 5,000 up to 1 in 1,000, for this purpose, and the method has met with some success. The risk of inducing argyrism must be borne in mind.

Olive-oil or almond-oil before meals may help, by reason of the inhibitory influence of fats on gastric secretion. Starting with a teaspoonful, the dose may be increased up to 1 ounce.

As to diet, I have followed the plan suggested by Walter Broadbent some years ago, based upon Pavloff's work, and that is to give the food in a form which will not excite more secretion of gastric juice than can be helped. There are five stages in the diet. I give the patient a paper with these stages written down, and I explain that if he is getting better, he can pass from 1 to 5, and that if he is not so well he should work in the opposite direction. In the first stage, which is seldom required except when there is ulceration, he is only allowed milk and cream. In the second, bread and milk and soft milk puddings, such as cornflour. Thirdly, bread-and-butter and eggs.

Broadbent says—although I have not found it so in all cases—that they are tolerated best in the form of buttered eggs, the butter still further diminishing the secretion of the gastric juice, while the large amount of protein in the egg will tend to fix the hydrochloric acid. Fourthly, fish and vegetables, and lastly meat; while we entirely forbid the use of meat-extracts of all kinds, because these stimulate the flow of gastric juice without giving anything for it to act upon. Such a scheme is useful in the treatment of hyperchlorhydria, enabling the intelligent patient to modify his diet according to the condition of his malady.

Physiological Principles in the Treatment of Gastric Ulcer.

During a period of eight years 428 cases were admitted to the medical wards of St. Bartholomew's Hospital as gastric ulcer, 366 being females and 62 males. Yet in the post-mortem room during the same period gastric ulcer was found in 20 females and 22 males. It is a striking fact that, while the mortality was almost exactly equal, there should have been so many more cases of hæmatemesis in young females, and one which lends some support to Hale White's contention that this symptom in young women is by no means always due to ulceration, but more often to a general oozing from the mucous membrane, for which he suggests the name of 'gastrostaxis.' Some such cases have been operated on for hæmorrhage, and no sign of ulceration has been found. It is difficult to exclude superficial erosions, however, even at operation. Some of them have had very

little gastric pain, and are usually amenable to treatment. The ones with a definite history of gastric pain are less amenable to treatment and more liable to relapse; these are probably cases of true ulceration. Moynihan has pointed out that in the early stages of a gastric ulcer, there may be a sense of prostration at just the interval after food at which pain subsequently develops. He further states that there is an interval of relief after food, unless the ulcer is close to the cardiac end. Both of these observations I can confirm. A useful distinction between gastric and duodenal ulcer is this: a light meal is followed by pain more quickly than is a substantial meal when there is a duodenal ulcer. With a gastric ulcer a substantial meal causes pain more quickly, while after a light meal pain may not occur at all. Now that we recognize that many cases previously diagnosed as gastric ulcer were suffering from something else, we must modify our views as to the success of medical treatment in gastric ulcer, and to recognize that relapse is frequent.

The orthodox treatment for hæmatemesis is to secure physiological rest for the stomach. After an initial injection of morphia, and a dose of 30 minims of adrenalin chloride solution in ½ ounce of water by the mouth, rectal feeding used to be started about twenty-four hours after the hæmorrhage.

Rectal Feeding.—Although rectal feeding has been practised since the time of Galen, its efficacy has not been established beyond cavil, and its limitations must be recognized. It is quite impossible to nourish the body by means of suppositories, which

in all probability cannot be absorbed at all. In some cases the rectum and colon have been found loaded with them at the post-mortem examination. As the large intestine is the principal place for the absorption of water, it is essential, if we are to have any success with rectal feeding, to take advantage of this fact by giving the nourishment in a fluid form. But even in this form its efficacy is open to doubt. The power of the large intestine to digest foodstuffs is very slight. Whether undigested albumen can be absorbed at all is merely of theoretical interest; it is certainly absorbed in much too small an amount to make it of any value if thus administered. Erepsin is the only proteolytic ferment secreted by the intestine which can break down proteoses and peptones into simpler bodies prior to absorption; it can only act on caseinogen and fibrin among the native proteins. As erepsin ordinarily acts after pancreatic juice, we should naturally predigest the proteins by liquor pancreaticus before administering it *per rectum*; this has a further advantage over merely peptonizing agents in digesting carbohydrates and fats also. Even when the rectal feed is completely pancreatized, it is doubtful how far it can be absorbed. Though the large intestine absorbs water readily, food is normally absorbed as completely as it can be in the small intestine. The highly specialized epithelium over the villi is the main agent in this. It is a pure assumption to conclude that the widely different epithelium of the large intestine can act in a similar manner. Yet the administration of small

nutrient enemata is based on that assumption. It has been claimed that the larger enema will get through the ileo-cæcal valve, and be absorbed in the small intestine. Church noted in a case of duodenal fistula that some of a soap-and-water enema reappeared through the opening. Charcoal particles administered in an enema have been found in the stomach. But we cannot rely on this regurgitation as a regular event. Boyd has looked carefully for it by the charcoal method, without success. Moreover, only large enemata can be expected to reach as high, and the larger the enema the more difficult it is to retain.

Turning from these *a priori* considerations to actual results obtained, I will first summarize some of the previous observations, and then my own experiments.

Absorption of Proteins. — Some observers have thought that quite large amounts of proteins were absorbed. But there was an important source of fallacy in the method employed; it was assumed that the nitrogen which could not be recovered from the bowel was assimilated. But it is notoriously difficult to recover everything from the bowel by washing it out. Even when daily irrigations have been given with scrupulous care, there may be days afterwards an evacuation of a large amount of highly putrid material. And in any case, some of the protein which disappears may have been reduced by putrefactive changes into a form in which it has no nutritive value.

Even assuming that all the nitrogen which could not be recovered had been assimilated, nitrogenous equilibrium could not be obtained during rectal feed-

ing, even in those who were accustomed to a diet poor in nitrogen (Boyd).

Laidlaw and Ryffel estimated the nitrogenous output in a case of rectal feeding during coma, and found that it was approximately equal to that obtained in the later stages of fasting—as, for instance, with the professional faster Succi, from the fifteenth to the twentieth day. The nutrient enemata in this case contained the white of nine eggs, 6 ounces of raw starch, and 24 ounces of peptonized milk in the day. It may be remarked that egg-white would not be readily absorbed, while it is doubtful if starch can be digested by the large intestine at all.

Absorption of Carbohydrates.—Normally, carbohydrates are absorbed by the bowel as dextrose, and of all the foodstuffs this appears to be the best utilized in rectal alimentation. Mutch and Ryffel advise 6 per cent. of dextrose in 15 ounces of tap water, six-hourly, with daily irrigation of the bowel four hours after the last dose. Using recovery methods, different observers claimed that 67 to 100 per cent. was absorbed. It has been urged that here again bacterial decomposition accounts for much of the disappearance of the carbohydrate. Boyd found, however, that the *Bacillus coli* could only account for the disappearance of about 1 per cent., but does not state whether the lactic-acid-forming organisms could not be responsible for more than this. That dextrose is definitely absorbed from the bowel is, however, proved by the following facts! Reach found that the respiratory quotient was raised by rectal feeds of dextrose—

a sure sign that they were being utilized—and ketosis has been abolished by this procedure. Nothing abolishes ketosis so rapidly as assimilation of carbohydrates, just as nothing causes it to appear so quickly as deprivation of carbohydrates.

Absorption of Fats.—No emulsion, however fine, is absorbed in the absence of splitting ferment. This ferment is normally supplied by the pancreatic juice, and in its absence we have to depend upon bacterial decomposition. It is a simple matter to provide the ferment by liquor pancreaticus, but even then absorption may be very imperfect. In one of Edsall's and Miller's cases only 18·61 per cent. of the fat was absorbed. The fat in the yolk of egg is considered to be better absorbed than other forms of fat, but, personally, I do not employ eggs in rectal feeding, for they add to the nursing difficulties, already sufficiently great. If any of the egg is returned, it is very offensive.

In a patient with a fistula of the thoracic duct, Munk and Rosenstein only found 8·7 to 5·5 per cent. of the fat given *per rectum* could be recovered. I have carried out rather similar observations on a case of filarial chyluria under the care of Dr. Samuel West. On an ordinary diet the urine was quite milky, and he was placed on a fat-free diet to relieve the pain and occasional hæmaturia caused by the passage of large fatty masses. The urine then became merely opalescent, but even the addition of milk to his tea caused an obvious increase in the fat in the urine. After determining the amount of bodies soluble in ether and the saponification value of the urine on the fat-free

diet, he was given an enema of 120 c.c. of olive-oil and 80 c.c. of a 2 per cent. solution of Na_2CO_3, which had been pancreatized for an hour. On another occasion he was given a pint of pancreatized milk *per rectum*. It happened that the saponification value and the ether-soluble bodies were actually lower in amount on the days when these enemata were given. This indicates that no fat was absorbed from these enemata by the large bowel.

Absorption of Salt and Water.—It is agreed that salts and water are freely absorbed from the large intestine, and the advantages claimed for rectal feeding are probably due to these ingredients. It is well known that the body can stand deprivation of food for a considerable time if these are supplied. W. Pasteur advocated the administration of 10-ounce enemata of plain water at a temperature of 100° F. every four or six hours. He claimed that the results were at least as good as with the ordinary nutrient enemata, while it is far simpler and pleasanter for the patient. Sharkey has used ½ pint of saline four times in each twenty-four hours, and has been equally impressed with the advantages of this method.

Nitrogenous Metabolism during Rectal Feeding.—My own observations have been chiefly directed to comparing the nitrogenous metabolism in patients on rectal salines and nutrient enemata. The nutrient enema which I have usually employed is composed of—

4 ounces of milk.	20 grains of bicarbonate of soda.
1 to 2 drachms of plasmon.	1 drachm of liquor pancreaticus.
1 to 2 drachms of dextrose.	5 minims of tinct. opii.

The liquor pancreaticus is allowed to act for twenty minutes at 37° C., the opium being added just before administration, with the object of increasing the tolerance of the bowel. The bicarbonate of soda is added to imitate the normal alkalinity of the pancreatic juice (1 per cent.). This enema is given every four hours, the rectum being washed out every night and morning. The total foodstuffs thus given in the twenty-four hours amount to—

Proteins	75	grammes.
Carbohydrates	75	"
Fats	27	"

This is clearly much less than the minimum required to keep the body in nitrogenous equilibrium, even supposing it were all absorbed, which is far from being the case, while its caloric value is only 866.

The larger enema—a pint of milk three times a day—has not yielded me very good results though recommended by some authorities, the patient usually failing to retain them after the first day or two. This would be equivalent to 68 grammes of each of the three foodstuffs, and its caloric value would be 1,188. I have no personal experience of the enema administered continuously drop by drop, but I have heard from those who have that it caused the patients so much discomfort that they were forced to abandon it. The enemata were administered in my cases by a soft rubber catheter attached to the barrel of a 4-ounce glass syringe, the contents being allowed to flow in slowly by gravitation.

When no nitrogenous food is taken there is a steady fall of nitrogen in the urine till the output reaches 5 grammes a day, and even lower. One of the first effects of giving nitrogenous food will be a rise in the nitrogenous output in the urine, as the greater part of the urea is exogenous—*i.e.*, comes from the food. The nitrogenous output in the urine will therefore be a more accurate criterion of the absorption of nitrogenous material from the bowel than the loss of nitrogen from the rectal washings, because it is evidence of actual assimilation. When rectal salines are given, there is a steady fall of urinary nitrogen. Starting with 10 grammes to 11 grammes the first day, it falls to about 5 grammes by the fifth day, and usually remains at that point, though in some of my cases it fell as low as 3 grammes, or even 2 grammes, a day. Acetone usually appears by the end of the first twenty-four hours, and diacetic acid within the next twenty-four hours. On comparing this with the cases where the standard enema was employed, hardly any difference was detected in the nitrogen output. There was a steady fall in the total nitrogen down to 5 grammes, and in one case as low as 4 grammes. The onset of acetonuria was, however, delayed as a rule, and it was usually less severe and of shorter duration. The great factor in the production of acetonuria is deprivation of carbohydrate, and as the enema contained both dextrose and lactose, the disappearance of acetonuria indicated that some of these were absorbed. In some cases acetonuria persisted throughout.

In one experiment salines were given till the nitrogen in the urine fell to 5 grammes. The standard enemata were then given for two days, but the nitrogen output was hardly affected at all. The same amount of food was given by the mouth, and the nitrogen output promptly rose.

Practical Deductions.—I think these results go to show that, if any protein food is absorbed from ordinary nutrient enemata, the amount is so little as to make it hardly worth while to subject patients to so much discomfort for so small an advantage. A gain in weight has been claimed as evidence of their value, but this has been observed also on rectal salines. The addition of 5 per cent. of dextrose to the salines is probably an advantage, as enough of it may be absorbed at any rate to check ketosis.

When one begins to doubt the efficacy of rectal feeding, the inconveniences associated with it assume a greater degree of importance. As disadvantages must be mentioned—(1) The thirst, which should be relieved by giving a rectal saline as well; (2) the difficulty in keeping the patient in a cleanly condition; (3) the secretion of gastric juice which it causes. The most conclusive evidence that this occurs is afforded by the observation of Umber, who found in a patient with a gastrostomy wound that the injection of food *per rectum* was followed by the secretion of an acid gastric juice. It is hardly securing a condition of physiological rest to allow this juice to be poured over an ulcerated surface without having

any food on which to act. To neutralize this juice I was accustomed to give the patient bismuth lozenges to suck. This serves both to neutralize the acid and to form a protective covering to the ulcer. At the same time, by keeping the salivary glands active, it diminishes the chance of (4) parotitis, which is due to an ascending infection of the salivary ducts. I am quite sure that in this way it is much easier to keep the mouth clean. Incidentally, I should like to protest against the use of glycerine in a mouth-wash for this or, indeed, in any other condition. The desiccation which follows only aggravates the state of the mouth. Ice is also objectionable; though pleasant at the time, it aggravates thirst. Plain hot water, to which a little potassium permanganate has been added, is, in my opinion, much to be preferred. (5) Persistent vomiting is an occasional complication in rectal feeding. If this starts, it generally persists until mouth-feeding is resumed. Unfortunately, it is often regarded as a sign that the stomach cannot tolerate anything, which is not the case. I believe it is due to the ketosis consequent on starvation. (6) The pronounced subnutrition induced by rectal feeding is very unfavourable to the healing of an ulcer in patients who are already in a poor physical condition consequent on one or more hæmorrhages, and may lead to serious inanition. Self-digestion goes on more rapidly in fasting than in well-fed tissues, and this may lead to extension of the ulcer and recurrence of the hæmorrhage. It is useless to think of building up a patient

by this method to a condition of improved nutrition prior to operation, for, say, an *impermeable* œsophageal or pyloric obstruction. I have only once tried this at the request of a surgical colleague, and I shall not repeat the attempt.

It seemed to me possible that better results might be obtained if, instead of merely peptonizing proteins, they were completely broken down into amino-acids, the form in which absorption normally occurs. Some preliminary experiments did not afford me much encouragement. Rendle Short and Bywaters, however, found that, by allowing pancreatic extract to act on milk for twenty-four hours, they could obtain decidedly more absorption. To each pint of milk they added an ounce of pure dextrose, and gave 5 ounces of this every four hours. I have used a Thermos flask as a convenient method of keeping up the pancreatic digestion for the required time. This plan is worthy of a trial in exceptional cases, and I have met with some success with it, but for the ordinary nutrient enema containing protein and fat there is, in my opinion, no place left to-day in therapeutics.

Immediate Feeding in Gastric Ulcer.

In 1901 Lenhartz protested strongly against the orthodox treatment for gastric ulcer. He urged that in patients who are already in a poor physical condition consequent on one or more hæmorrhages, and, indeed, often collapsed, the 'starvation treatment'

maintained their wretched anæmic state, and might produce a serious state of inanition, very unfavourable to the healing of an ulcer. On the other hand, if enough milk were given by the mouth to maintain the body-weight, it would overfill the stomach and stretch its walls, thus preventing contraction of the ulcer and tending to renewal of the bleeding.

He maintained that the correct principles were—

1. To promote healing by providing adequate nourishment.

2. To prevent distension of the stomach by limiting the size of the meals and the amount of fluids; and by the application of ice to the epigastrium.

3. To prevent the action of the excess of hydrochloric acid by combining it with food albumen and with bismuth.

These indications are best fulfilled, in his opinion, thus: Feeding by the mouth is started at once, concentrated foods rich in albumen being employed. Food is given at hourly intervals from 7 a.m. to 9 p.m., but complete rest is allowed at night. The patient is fed a teaspoonful at a time, and is not allowed to feed herself for a fortnight. She is kept in bed for a fortnight, and other medicinal measures, such as the administration of bismuth, can be employed as required.

Essentially the diet consists of iced fresh milk and raw eggs, the whole egg being beaten up and iced. Both milk and egg are prepared in a covered glass tumbler surrounded by ice. The feeding-spoon is also kept iced. Granulated sugar is added to the eggs on

the third day; later, raw scraped beef, boiled rice, and soaked rusk are also given.

No attempt is made to provoke an action of the bowels during the first week at least, to avoid peristalsis, and allow absorption of outpoured blood in the intestines. Then, if necessary, a small glycerine enema or hot-water enema may be used.

The advantages claimed for this treatment are that recovery is more rapid, and that it does not deplete the patient, the food-supply being sufficient throughout. The sour regurgitation subsides, vomiting and bleeding stop more quickly, and relapse is less frequent, while pain ceases promptly, and morphia is never needed; it is possible to treat the anæmia earlier, and an increase in the body-weight may be manifest as early as the first week.

One important modification I have found advisable to make. Cases in which active ulceration is present usually do not tolerate the raw meat as early as the sixth day, and I do not think it wise to make them try and do so. Pavloff showed that meat-extracts were active stimulants to the secretion of acid in the gastric juice, and our object in these cases is to avoid hyperchlorhydria, while fixing such acid as is present by combining it with protein. The nourishment in the 86 grammes of beef can be readily obtained in a less stimulating form by adding 2 drachms of a milk protein, such as plasmon or protene, to the diet.

Another minor modification of the original dietary in which I have followed Lambert is the substitution

MODIFIED LENHARTZ DIET.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Eggs	1	1½	2	2½	3	3½	4	4	3	3	3	2	2	2
Milk (ozs.)	3	4½	6	7½	9	10½	12	17	18	19	20	21	22	23
Total bulk of egg and milk together (ozs.)	5	7½	10	12½	15	17½	20	25	25	25	25	25	25	25
Glaxo, half strength (ozs.) ..	5	7½	10	12½	15	17½	20	25	25	25	25	25	25	25
Sugar, half in Glaxo (drs.) ..	—	—	6	6	8	8	12	12	14	14	14	14	14	14
Plasmon (drs.)	—	—	—	—	—	2	3	3	3	3	3	3	3	3
Blancmange (ozs.)	—	—	—	—	—	—	—	3½	3½	7	7	10	10	10
Rusks (ozs.)	—	—	—	—	—	—	—	—	¾	1½	1½	2½	3	4
Pounded fish	—	—	—	—	—	—	—	—	2	2	2	2	2	2
Butter (ozs.)	—	—	—	—	—	—	—	—	—	¾	1½	1½	1½	1½
Quantity given each feed (ozs.)	1	1½	2	2½	3	3½	4	5	5	5	5	5	5	5
Calorie value approx. ..	106	240	400	475	580	685	825	1,115	1,185	1,650	1,820	2,010	2,080	2,200

Glaxo, half strength, is given in alternate feeds.

Ten feeds in 24 hours = 2-hourly by day, 4-hourly by night.

To relieve thirst: saline enemata, ½ pint twice a day if necessary, or 1 oz. of water by mouth occasionally after second day.

Enema saponis every other day or daily if necessary; olive-oil enema at night, enema saponis in morning occasionally if required.

Mouth swabbed out before and after feeds with solution of sod. bicarb., 7 dr. to 5 ozs. of water.

of cooked minced chicken for the raw ham, which, however suitable for German patients, is not grateful to English palates. I have also given rectal salines, if required, to relieve thirst. The modified Lenhartz dietary given on p. 87 is the one now used as a routine at St. Bartholomew's Hospital and has the advantages of less frequent feeding and avoiding the large number of eggs given in the original scheme.

Lenhartz found that in the 100 cases treated before he introduced this method, recurrence took place in 20 per cent., but after introducing this treatment recurrence occurred in only 8 per cent. The method has been taken up on the Continent to a considerable extent and also in America, but up to a few years ago it had made very little headway in England. There was considerable prejudice against it at first, but it is now rapidly becoming the orthodox method. I have used it since the beginning of 1908 and will give the results in my first thirty hospital cases. There had been recent hæmorrhage in seventeen out of the thirty cases. In one case it is probable that the hæmorrhage was from cirrhosis of the liver, but I could not be certain as to the source, and I have included it. The treatment was quite satisfactory in twenty-two cases. The result was unsatisfactory in four, and there was recurrence of the hæmorrhage in four others. In one there was recurrence subsequently with nutrients, just as with Lenhartz treatment. In another the recurrence was very slight, amounting to the regurgitation of a

drachm of blood. In a third case, with a history of sixteen years, recurrence had previously taken place on nutrients. Gastro-jejunostomy was performed, and the hæmorrhage recurred a few months after the performance of that operation. Finally, an ulcer surrounded by dense adhesions to the liver had to be excised, and the patient made a good recovery. In another case recurrence took place, and gastro-jejunotomy had to be performed for a chronic ulcer. Unfortunately, the patient died of peritonitis, the direct result of operation. As to the four which I have classified as unsatisfactory, apart from recurrent hæmorrhage, one discharged himself on the fourth day —a thing which is common enough in patients treated by nutrients. In one case there was mucous colitis also. With this complication the treatment of the gastric condition, which I believe to be secondary, is often of no avail. Another case was that of a neurotic alcoholic lady, on whom I tried it simply because no other treatment of her gastric pain had done any good. In the fourth case, although there was great temporary relief, the X rays showed an hour-glass stomach, for which operation had to be performed. Here, too, there were dense adhesions, and a gastric fistula formed, with fatal results. Clearly the fatalities had nothing to do with the Lenhartz treatment; they were both in cases of long standing, and would not have been avoided by rectal feeding.

I have been favourably impressed by the method, and I am supported by my house-physicians and the

sisters in charge of the cases, who would much rather have to deal with a case treated on this plan than on the other, avoiding, as it does, the misery of starvation and all the discomforts of rectal feeding. The method is peculiarly suitable for the conditions of private practice. Nutrient enemata require time and skill in their preparation. We cannot expect them to be given properly except by a trained nurse, whose services cannot always be afforded. But in this method we have a simple, safe, and effective treatment, which is free from any disagreeable features.

The use of horse-serum has been advocated by Hort and others for gastric or duodenal ulcer. One of the many functions of serum is the restraint it exerts on the autolytic action of the tissue cells. As autolysis goes on more rapidly in fasting than in well-fed tissues, there is a rational basis for the use of horse-serum in a disease for which most methods of treatment entail more or less starvation. The antipeptic action of serum depends chiefly on the serum-albumen it contains, and Hort has prepared a serum in which this constituent is specially increased in amount. It can be given in daily doses of 30 to 40 c.c., but it must be fresh and sterile, and should be given directly after food, when absorption is at its height. I have not been greatly impressed by the results, and when starvation methods are not used serum is less often called for.

The later results of gastric ulcer are chiefly due to the mechanical difficulties produced by scar tissue, such as

pyloric obstruction and hour-glass stomach. They may, therefore, be more conveniently considered in the next chapter.

APPENDIX TO CHAPTER II.

Examination of the Gastric Contents.

That doubts are so often thrown on the value of a chemical examination of the gastric contents is due in many cases to the fact that defective methods have been employed. It is not sufficient to test qualitatively for free hydrochloric acid, and then take the total acidity as a measure of the physiologically active hydrochloric acid, though even this gives important information.

The test-meal I employ is $\frac{3}{4}$ pint of tea without milk or sugar and a round of dry toast, which is quite satisfactory as an excitant of gastric secretion. The contents of the stomach are withdrawn one hour later. For this I always employ Senoran's bottle, which is simple and efficient, and overcomes any difficulty in starting the syphonage. The patient should be sitting up, with the head rather forward. The natural tendency is to throw the head back, but there is less difficulty if the head is tilted forwards. The tube is lubricated by being simply dipped into hot water and passed as quickly as possible, the patient being directed to swallow it, while the first finger of the left hand is used as a guide. The distance from the teeth to the stomach is generally $15\frac{3}{4}$ inches, which is just under

40 centimetres. The tube is passed till the 45-centimetre mark on it is level with the teeth. With the tube in position squeeze the bulb, and then, before releasing, put the thumb or finger over the little hole in the side of the bottle-neck. There is then an efficient suction action in the tube, and the contents of the stomach are speedily extracted into the bottle. If you do not withdraw enough, repeat the squeeze, taking care to remove the thumb until you let go of the bulb, or else air will be driven into the stomach, which is uncomfortable. The bottle is provided with a rubber band to close the hole, and a rubber stopper to make it portable.

The contents of the bottle are filtered and some of the residue examined microscopically. If starch digestion is very incomplete, it points to excess of acid, which stops the ptyalin of the saliva too soon. If the contents are frothy, it suggests carcinoma. The presence of the long, non-motile Oppler-Boas bacillus is said to be specially diagnostic of gastric carcinoma. Really it means there is no free hydrochloric acid, which is commonest in carcinoma. It is a lactic-acid-producing organism, and, according to some, it is the same as the Bulgarian bacillus, of soured-milk fame. The presence of sarcinæ is believed to be a sign of dilatation of the stomach. No importance should be attached to the presence of yeast, which merely comes from the bread.

Gunzberg's is the most reliable qualitative test for detecting free hydrochloric acid. 'The best way of

applying the test is to keep the phloroglucin and vanillin in bottles to the corks of which are attached little scoops which will measure about 4 grains of the former and 2 grains of the latter. These quantities are placed in a dry porcelain evaporating-dish with 1 c.c. of alcohol (pure methylated spirit does quite well), and then about 2 c.c. of the filtered gastric contents are added. The dish is heated on the water-bath till its contents are nearly dry. A brilliant scarlet-red colour indicates free HCl; a yellow colour is negative' (Willcox).

Total acidity is determined by titration with a decinormal alkali, using phenolphthaleïn as an indicator.

The amount of physiologically active hydrochloric acid is the most important point, and this can best be determined by Willcox's method. The principle of it is as follows: In the gastric contents hydrochloric acid may exist in three forms—

1. Free HCl .. .. ..
2. Combined HCl:
    (*a*) With proteins and nitrogenous organic bases .. — Physiologically active.
    (*b*) With inorganic bases, as sodium chloride.

The presence of free HCl is not of more importance than that of the combined acid. The latter, which is combined with protein and nitrogenous organic bases, is acid that was free a short time before, but has now begun its duties in the process of digestion; it is, therefore, of equal importance with free HCl.

Now, if we estimate the total chlorides in a sample of gastric juice, and in another estimate the chlorides present after charring—*i.e.*, the inorganic chlorides—the difference between these two results gives the amount of physiologically active HCl.

The estimation is carried out as follows, but I am accustomed to use half the quantities given here: 'Two equal volumes of the filtered gastric contents (20 c.c.) are taken.

'(*a*) One portion is diluted with about 40 c.c. of distilledwater, 10 c.c. pure nitric acid added, and about 5 c.c. of solution of iron alum. A measured excess (30 c.c.) of decinormal silver nitrate solution is added. Decinormal ammonium sulphocyanide solution is run in from a burette until a permanent reddish-brown tint just results. The difference between the quantity of silver nitrate solution added and the ammonium sulphocyanide solution used gives the amount of total chlorides present as decinormal hydrochloric acid.

'(*b*) The other portion of the gastric contents (20 c.c.) is placed in a platinum evaporating-basin, and evaporated to dryness on a water-bath; the solid residue is heated for about an hour on the water-bath, and the dish is then placed on a piece of wire gauze and heated with a small Bunsen flame, the flame not coming into actual contact with the basin. The heating is continued for about ten minutes until the residue is well charred. The dish is cooled, about 60 c.c. of water and the pure nitric acid are added, the contents being well stirred with a glass rod. The titration is performed exactly as in (*a*), and the quantity of chlorides present is given in terms of decinormal hydrochloric acid. The difference between the chlorides present in (*a*) and (*b*) expresses with great accuracy the amount of the physiologically active HCl.'

[For a fuller account of methods, see Willcox, Transactions of the Pathological Society, vol. lvi., p. 250; and Harley and Goodbody, 'Chemical Investigation of Gastric and Intestinal Diseases' (Arnold).]

The following figures illustrate the results obtained in some typical cases:

	Gunzberg's Test for Free HCl.	Physiologically Active HCl.	Mineral Chlorides.	Total Chlorides.	Ratio of Active to Mineral.
		Per Cent.	Per Cent.	Per Cent.	
Normal	+	·2	·1	·3	200/100
Cancer .. .. {	−	·01	·17	·18	[illegible]
	−	·075	·210	·294	[illegible]
Chronic gastritis ..	+	·14	·12	·26	[illegible]
Simple hyperchlorhydria	+	·34	·076	·416	[illegible]
Duodenal ulcer	+	·301	·1	·401	[illegible]

CHAPTER III

MECHANICAL FACTORS IN DIGESTION AND INDIGESTION

It should hardly be necessary to insist on the cardinal importance of the teeth in the due performance of mastication, without which the food cannot be insalivated. It may appear paradoxical to assert that the inevitable tendency to swallow soft carbohydrates is a more serious consequence of defective teeth than the bolting of meat. Yet I believe this to be the case, for, as explained already, carbohydrates are not then digested in the stomach, where they are apt to ferment and produce flatulence.

Deglutition.—The act of swallowing consists of three stages, the first of which is voluntary, the food bolus being thrust between the pillars of the fauces by the tongue. After this all voluntary control over the movements of the alimentary canal is lost until the rectum is reached. The contact of the food against a specially sensitive spot on the back wall of the pharynx starts the subsequent stages. We have only to swallow several times in rapid succession until no more saliva is present in the mouth to realize how impossible the act becomes in the absence of a peripheral stimulus. The second

stage is a rapid reflex, rapidity being necessary, as the pharynx is common both to respiration and alimentation. The upper and lower parts of the respiratory tract are shut off by the elevation of the soft palate, by pulling up of the larynx under shelter of the epiglottis, and the approximation of the vocal cords. The importance of these protective movements is seen in the regurgitation of fluids through the nose when the soft palate is paralyzed by diphtheritic neuritis, and in the dysphagia which results from the destructive tuberculous ulceration of the epiglottis.

The constrictors of the pharynx are now drawn over the food bolus, which is thus forced into the œsophagus. Here the third stage of deglutition begins, a slow peristalsis which depends on the vagus as far as the striped muscle is concerned, and on local nervous mechanisms for the plain muscle. In the swallowing of liquids, however, there is no need for peristaltic waves, the œsophagus remaining dilated and passive. During swallowing a pressure develops in the closed mouth equal to 20 centimetres of water, while immediately afterwards the stomach relaxes, the intragastric pressure falling almost to zero, which is sufficient to direct the stream of fluid into the stomach. Hence, when corrosive acids have been swallowed, the lesions are produced in a patchy manner, which would not occur if the fluid were forced down by a peristaltic wave. The passage of fluid down to the stomach takes four to eight seconds, half of which time is occupied in passing through the cardiac sphincter.

Solids require the aid of peristalsis, and take eight to eighteen seconds if well lubricated, but a dry bolus may remain above the cardia for many minutes (Hurst). The peristaltic wave can act against the force of gravity, for swallowing can be accomplished in the inverted position, though more slowly.

The different conditions obtaining in the swallowing of liquids and solids explain some of the symptoms in malignant stricture of the œsophagus. At the necropsy it may appear as if there could have been no difficulty in swallowing food or in the passage of a bougie, but, of course, much of the obstruction is due to spasm. It is common for the dysphagia to begin suddenly during a hearty meal. A spasm has been evoked and will recur on each attempt at deglutition. I have seen the same thing occur in congenital œsophageal stricture. As the act of swallowing liquids excites no spasm, but rather an inhibition of peristalsis, it is easily performed long after all solids are unable to pass. It is important to note that a spasm may result from a growth lower down the œsophagus or at the cardiac orifice, which, like the gastric spasm to be referred to later, is presumably protective in nature.

Just as acid in the duodenum keeps the pyloric sphincter closed, so acid in the stomach keeps the cardiac sphincter closed. This is a great advantage, for the gastric contents are nauseating in odour and highly disagreeable to the taste. But when the intragastric pressure rises above 25 centimetres of water eructation or regurgitation occurs, to be followed

promptly by œsophageal peristalsis forcing back any food into the stomach again. In œsophagismus, there is a failure on the part of the cardiac sphincter to relax rather than an active spasm (Hurst). It may depend on some irritable focus further down the alimentary tract. The accentuation of the symptoms by acid dyspepsia is similarly explained as an exaggeration of the ordinary effect of acid in keeping the cardiac sphincter closed. Conversely, Kast has suggested that the disagreeable taste in the mouth and the furred tongue of gastric disturbances is due to the adhesion to its rough surface of partly digested pieces of food, leucocytes, and epithelial cells, which have come back from the stomach. Such symptoms are commonest in the fermentative dyspepsia associated with deficiency of HCl, which is precisely the condition for a relaxed cardia. The triangular distribution of fur on the back of the tongue is characteristic of this.

The Stomach.

The movements of the normal stomach have been described in the previous chapter.

Spasmodic Hour-Glass Contraction.—This condition is liable to be mistaken for an organic hour-glass contraction. Jellasse, in 1906, suggested, and it is generally agreed, that a spasmodic ring of constriction is most usually due to the presence of an ulcer, which is generally situated on the lesser curvature, and may be quite small. But it may occur in other conditions. Thus,

I had a case associated with old appendicitis, in which the spasm could be seen gradually to relax under anæsthesia. I believe that the symptoms in so-called 'appendix dyspepsia' are in part, at any rate, due to such reflex spasm. The spasm can sometimes be made to disappear by abdominal massage, by vigorous voluntary contractions of the abdominal muscles, and less frequently by the injection of $\frac{1}{100}$ grain of atropine. The contracted area varies in degree; there is no sagging or peristaltic wave in the proximal half of the stomach. These three points serve to distinguish spasmodic from organic constriction. It must be remembered, however, that a partial organic hour-glass constriction due to an ulcer which is still active may be rendered complete by the supervention of spasm, so that stenosis, thought to be severe from the X-ray examination, may be found to be comparatively slight at the operation.

Hurst describes two other conditions as 'functional' hour-glass stomach. One is due to the combination of severe atony with gastroptosis, in which the passage between the more fixed fundus and the dependant part of the stomach becomes much narrowed by the dropping of the latter. But this appearance completely vanishes in the recumbent posture, and he therefore terms it 'orthostatic.' To the other form, the term 'functional' is hardly applicable. It is due to an ulcer on the lesser curvature which has become adherent to the left lobe of the liver. When the

patient stands up, the rest of the stomach tends to assume a vertical position, but the adherent part being fixed, a line of tension is produced diagonally across the stomach, dividing it into two parts. But here, again, the constriction disappears on lying down. Incidentally I may say that this form is resistent to medical treatment, and offers considerable difficulties to surgery. Strictly speaking, it should be classed among the perigastric adhesions.

True Hour-Glass Stomach.—Extended use of X rays has shown that this condition is a commoner sequel of gastric ulcer than was supposed. Apart from the characteristic skiagram, the chief signs are those described by Moynihan. When the stomach is washed out, part of the fluid is lost, and conversely there may be a sudden reappearance of stomach contents after lavage. When the stomach has apparently been emptied, a succussion splash may still be elicited by palpation of the pyloric portion. If the stomach is distended by carbon dioxide, gurgling or bubbling sounds may be heard at a point distinct from the pylorus, and after this distension two swellings with a notch between can sometimes be made out. Only operative treatment can be effective.

Perigastric adhesions are now well recognized as a mechanical cause of indigestion. There is generally a previous history of gastric ulcer or biliary colic; the pain is much influenced by the position of the patient and little by diet; and local tenderness is

common, while vomiting is rare (E. P. Paton). To this we may add that the X rays show the stomach to be held up somewhere, so that the normal alterations in its position on change of posture or on vigorous contractions of the abdominal wall do not occur.

A woman of thirty-eight was admitted under my care for abdominal pain, situated just below the costal arch, and a little to the left of the middle line. In the eight years previous she had had several attacks of severe pain after food, accompanied by vomiting. For the past few weeks she had suffered from what she described as a 'different pain,' which was 'dragging' in character, localized, and not related to food, but coming on as soon as she adopted the erect position. A test-meal showed a total acidity of 0·29 per cent., with presence of free hydrochloric acid. No organisms were found. A skiagram showed that there was no dilatation of the stomach, but that the organ was held up unusually high.

Now, although a succession of gastric ulcers may occur in a young woman, an eight years' history of gastric pain and vomiting in a woman of thirty-eight suggests one chronic ulcer that will not heal. But that active ulceration was still present seemed unlikely in the absence of (1) vomiting; (2) any relationship of the pain to food; (3) marked hyperchlorhydria. It appeared more probable that the symptoms were due to the result of old ulceration in the form of an adhesion

which became dragged upon in the erect posture. Such an adhesion could hardly be in the neighbourhood of the pylorus, for it had led to no dilatation of the stomach. The position of the pain further indicated the fundus as its site.

Sir C. Gordon Watson operated and found adhesions surrounding an old ulcer, the floor of which was formed by the anterior abdominal wall. The patient made a good recovery. I have also seen a perigastric adhesion involving the transverse colon, which yielded an unmistakable skiagram.

Dilated Stomach.—There are important differences between the atonic and the obstructive form of dilatation:

1. *Atonic Dilatation.*—There is sometimes a long history of chronic gastritis; or of a disease like typhoid fever which leads to muscular enfeeblement. But the most frequent cause is an emotional one which leads to sympathetic irritation. This would check gastric peristalsis and cause pyloric spasm. To such cases the term 'atonic' is not really appropriate. I have met with instances in which both father and son suffered from it. One of the most characteristic symptoms, which can generally be elicited on inquiry, is that the patient feels full up as soon as he starts eating. Hurst points out that both the atonic stomach and the contracted stomach give rise to this sensation. The contracted stomach feels full up because it cannot expand. The atonic stomach feels full up because it is already dilated, and the normal relaxation of the stomach as it fills, which avoids a rise of intragastric pressure, cannot take place. As soon as food is taken

into this relaxed stomach the pressure begins to rise and the patient feels full. After taking food there is a general sense of misery and discomfort rather than actual pain. The patient frequently complains of a disagreeable taste in the mouth, and there is often a brown fur on the back of the tongue, probably due to regurgitation of the contents of the stomach through a relaxed sphincter. There is seldom vomiting. Pyorrhœa is very common. On inspection of the abdomen there may be some dropping of the stomach, a hollowing out under the costal margin, and a fulness below and to the left of the umbilicus.

A succussion splash which is elicited only on deep palpation is only significant at a time when the stomach should be empty. A superficial splash has some significance. It is suggestive of atony, but it is sometimes distinguished with difficulty from the splash obtained in the colon. And neurasthenics and hypochondriacs have an extraordinary power of producing splashing by vigorous contraction of the abdominal walls. The two halves of a seidlitz powder, dissolved separately in water and swallowed, produce a distended resonant area distinctly lower than it should be. The test-meal may show diminished hydrochloric acid, in the cases following gastritis, but not in the nervous type, where in my experience hyperchlorhydria is commoner. An atonically dilated stomach gives, on X-ray examination after bismuth, a shadow reaching some distance below the umbilicus, with a broad meniscus at the bottom and a flat upper surface. Peristaltic waves are feeble or absent. Gastro-jejunostomy

will not be of any service, though if there is so much dropping that there is actual kinking of the pylorus, which really adds an obstructive feature to the atonic case, an appropriate abdominal support, such as Curtis', may be decidedly helpful.

We must distinguish between dilatation and gastroptosis, which is usually part of a general enteroptosis. In the latter the stomach is increased in the vertical diameter, whereas in the dilated stomach it is increased in the horizontal diameter.

Treatment.—Acute dilatation is a dangerous condition of toxic origin, in which treatment appears to be of little avail. Chronic dilatation may exist unsuspected in an alcoholic subject. In the ordinary dyspeptic type there has usually been a long-continued mucous gastritis. Treatment is likely to be ineffective in this type if lavage be not performed at the outset; otherwise our remedies are apt to be lost in the fermenting slimy mass that is already there. Sodium bicarbonate should be added to the water because of the solvent action of alkalies on mucus. The last part of the fluid employed may have an antiseptic added, such as a 2 volumes per cent. of hydrogen peroxide or a weak solution of potassium permanganate. The best diet is one that will not ferment easily. For this reason starchy foods are contra-indicated; they should certainly never be given in the form of pap, as is so often done. Dry toast, biscuit, or rusk, are preferable, because in the act of mastication some of the starch will become converted into malt-sugar; but any form of starch should be reduced to a minimum.

As Sir Clifford Allbutt says, 'There is no superstition more tenacious of life than that which prescribes carbohydrates to all dyspeptics as "so digestible," and into weak stomachs, ready to dilate, is thrown a mass of such a dish as rice-pudding—a bulky food, imperfectly salivated and peculiarly apt to decompose with the disengagement of volumes of carbonic acid gas.'

In bad cases I have restricted the diet, at first, to meat-juices and meat-extracts (because of their stimulating effect on the secretion of hydrochloric acid), and to lightly cooked minced meat, which does not ferment, and leaves but little residue. From the rapidity with which egg-albumen leaves the stomach it might be imagined that eggs would be a suitable diet in this condition; but patients generally protest that they cannot digest them. Some cases have improved on a Lenhartz diet. After food, hydrochloric acid or oxyntin (acidol) should be given, combined with arsenic and strychnine, which seem to have a tonic effect on the gastric musculature. In the nervous type, alkalies with bromide will do more good than acids, while the emotional cause will require investigation.

Abdominal massage is useful, as it increases peristalsis in the stomach. Rest after meals should be enjoined, since exercise immediately after can be shown to delay the discharge of food from the stomach.

2. *Obstructive Dilatation.*—The characteristic symptoms are vomiting of large amounts and steadily increasing discomfort between the attacks. After the

stomach has been emptied by a large vomit, the patient is comparatively comfortable for hours or even days, and then discomfort begins and increases until it culminates in vomiting again. A point of practical importance which I have found is that the vomit is highly acid, if the obstruction is not of a malignant nature. Ordinarily, though the secretion of gastric juice may be normal or even slightly hyperacid, the vomit will not show free hydrochloric acid because the conditions which excite vomiting are almost certain to have previously inhibited gastric secretion. But when there is obstruction to the pylorus the vomiting occurs from quite a different reason. Secretion has been taking place as usual, but onward progress and consequent neutralization are delayed so that the vomited contents will be highly acid. A young lady, who had had symptoms of gastric ulcer on two occasions some years before, suffered from paroxysms of vomiting. Between the attacks she seemed quite well. The vomit had an acidity equal to 0·292 per cent. HCl, which is distinctly higher than that shown by the ordinary test-meal removed with the tube. So that I felt sure that, whatever else there was, she had obstruction to the pylorus, which X-ray examination, and finally operation, showed to be the case. When there is obstructive dilatation, X rays show vigorous peristaltic waves in the stomach, but no onward progress of the bismuth into the duodenum.

Here the operation of gastro-enterostomy is definitely indicated.

Gastro-Enterostomy.—Increased knowledge of the gastric movements has shown clearly the limitations of this operation. It does not 'drain' the stomach. In quadrupeds and in man lying on his left side the pylorus is the highest point, and yet the stomach empties itself. Even when the body is upright and the gastro-enterostomized stomach is filled with water, the water does not run out, because the hydrostatic relations in the abdomen counteract the effect of gravity. Material does not move along the alimentary canal unless the pressure is greater on one side than on the other, and for this muscular contraction is necessary. Kelling performed gastro-enterostomy on dogs by all known methods. At the same time he made a duodenal fistula, which enabled him to observe that nothing escaped by the new opening or ostium. Even when the pylorus was partly occluded, the food passed through it rather than through an opening remote from the greatest pressure. Berg operated on two cases of duodenal fistula, and had a similar experience. In both gastro-enterostomy was done, but the discharge of chyme through the fistula ceased only in one in which he tied the pylorus as well. We are not justified in assuming that the region between the new opening and the pylorus is placed completely at rest. The full benefit of the operation is therefore obtained only in cases of definite obstruction to the pylorus. There is no doubt, however, that chronic ulceration with recurrent hæmorrhage has been benefited by it even when there was no pyloric obstruction. To under-

stand this, we must bear in mind the effect of the hyperchlorhydria associated with gastric and duodenal ulcer. Bolton has proved experimentally that hyperacidity facilitates the production and prevents the healing of a gastric ulcer. One of the actions of the acid when it enters the duodenum is to cause closure of the pyloric sphincter, which lasts until the pancreatic juice has neutralized it. Excessive acidity provokes excessive contraction, thus increasing the pain. Further, by keeping the chyme in contact with the pyloric glands the continued secretion of acid is stimulated. Thus, the excessive acidity causes pyloric spasm, while the spasm leads to increased acidity. The most intense pyloric spasm I have ever seen has been in fatal cases of hydrochloric acid poisoning. This spasm is responsible for the invariable occurrence of ulceration and ultimate stenosis in the neighbourhood of the pylorus in patients who survive long enough.

After gastro-enterostomy hyperchlorhydria usually passes off, though in exceptional cases a jejunal ulcer may follow, showing that the acidity has persisted. The diminution in acidity results from: (1) Regurgitation of alkaline bile and pancreatic juice into the stomach through the new orifice, which is not provided with a sphincter. (2) Absence of the chemical stimulant to gastric secretion, since the food is not kept in contact with the pyloric glands. That the secretion is diminished and not merely neutralized is shown by the reduction of the total chlorides in the

gastric juice. Retention of food in the stomach with repeated vomiting, the so-called 'vicious circle,' is an occasional bad result of the operation. This is not due to the repeated entrance of the food from the duodenum into the stomach, but to an obstructive kink or other demonstrable obstacle. Although, according to Cannon, sharp turns in the intestine are normally straightened without difficulty by the material driven on by peristalsis, this force is not at hand to straighten a kink immediately beyond the ostium. For the division of the circular muscular fibres at the operation has abolished the peristaltic wave there. The rational procedure is therefore to attach a narrow band of the distal gut continuously to the stomach wall for an inch or so beyond the ostium. The gut is then kept straight throughout a distance which permits peristalsis to become an effective force. When food passes into the proximal loop, as it often does, a peristaltic wave starts which drives it back again into the stomach, for as the circular muscular coat of the gut is not complete at this point, it is not driven into the distal gut. This must, at any rate, mix some of the food thoroughly with the digestive secretions poured into the duodenum. Distension of the stomach will also interfere with the proper action of the ostium by flattening out the gut wall until the entrance into the lumen of the intestine is changed into narrow slits.

Another unfavourable result may be too rapid drainage of the stomach as shown by Hurst. The chief

symptom complained of is a feeling of fulness slightly lower down than the site of the discomfort before the operation. The distension of the jejunum is probably responsible. The patient has generally found that a dose of castor-oil shortens the duration of this discomfort, because it hastens the onward progress of the contents of the distended jejunum. Hurst advises the recumbent posture after meals in these cases to delay the emptying of the stomach. If this is not sufficient, small doses of belladonna to relax the muscle-fibres of the intestine, and of codeine to diminish the excitability of the sympathetic nervous system, should be given half an hour before meals. I have found an abdominal support often helps to prevent this jejunal distension. Another exceptional cause of continued trouble after gastro-enterostomy is that the opening may have been made above the upper level of the gastric contents. This can be overcome by an abdominal support, and by the recumbent posture on the left side after meals.

The possibility of these various untoward consequences renders the operation far from an ideal one, but if the principles laid down here are followed, great benefits may be obtained in suitable cases.

Congenital Hypertrophic Stenosis of the Pylorus.— This cause of vomiting and marasmus in infants presents some interesting problems. The diagnosis rests upon the combination of vomiting, constipation, and wasting with visible peristalsis of the stomach and a palpable pylorus. That the condition may

really be congenital is proved by its having been found in a seven months fœtus, but the vomiting usually begins about the fourth week, and not later than the ninth week, after birth. It is generally sudden, copious, and forcible, so that a quantity representing more than one feed may be shot out a foot or more from the mouth, and perhaps through the nostrils also. With increasing dilatation the vomiting becomes less frequent, while the amount becomes greater. For the two characteristic signs of visible peristalsis and palpable pylorus, Still lays great emphasis on the importance of examining the abdomen immediately after feeding. It is then, and sometimes only then, that the abnormal peristalsis can be seen, and that the thickened pylorus can be felt. It may be necessary to examine for ten to fifteen minutes before the signs can be elicited. Sometimes the waves appear spontaneously, at other times only after repeated stroking or gentle kneading of the epigastrium. Post mortem the stomach is found greatly dilated, and the pylorus is much thickened for about ¾ inch, yet a probe can usually be passed through it readily. Microscopically, the only change found is hypertrophy of the muscular tissue.

The pathology of the condition is a vexed question. Congenital stenosis appears to be a misnomer, since the hyperplasia may occur after birth, and there is no true narrowing of the lumen. Pyloric spasm leading to muscular hypertrophy seems to be the sequence of events. But what causes the spasm? John Thomson suggests that it is due to an inco-ordination of the

muscles of the stomach, the central nervous system having not yet acquired proper control. It would thus be comparable to the stuttering of a child who is learning to talk. Edkins has made the interesting suggestion that this spasm, like many others, is protective. If there were pancreatic inadequacy, the acid, passing into the duodenum, would not evoke secretion from the gland, and would not be neutralized. The pyloric sphincter would, therefore, be kept firmly contracted. In this way food is prevented from entering a region where it could not be properly digested. In support of this hypothesis it may be pointed out that in young infants pancreatic inadequacy is the rule, so far as the starch-splitting ferment is concerned, and an extension of this inadequacy to the other constituents of the juice is a plausible conjecture.

Treatment.—With the improvement in surgical technique there can be no doubt that as soon as the diagnosis is made Ramsted's operation should be performed. The stomach should be washed out through a No. 15 catheter first to remove curds and other food residues. The injection of a solution of glucose *per rectum,* or into the loose tissues of the axillæ, diminishes the risk of acidæmia, and keeping the infant very warm during and after operation lessens shock. A combination of local with general anæsthesia appears to be favoured by surgeons. Both speed and gentleness are essential. The operation simply consists in a clean cut through the peritoneal and muscular coats along the white non-vascular line

on the pylorus, allowing the mucous membrane to herniate through the muscles. There is an unexplained liability to hyperpyrexia after operation, which may be due to the excessive zeal in trying to prevent shock. The troublesome and even dangerous diarrhœa which may follow operation is probably due to its having been delayed until the intestine has become atrophic, or to the bulk of the feeds having been increased too quickly. For it is essential that food should be given frequently in quite small amounts, beginning with not more than a teaspoonful at a time, while it is probably wise not to give any milk in the feeds for thirty-six hours.

Whey and raw-meat juice are apparently the best foods to start with.

If for any reason operation is decided against or declined, systematic lavage should be resorted to. Still formerly advised that the stomach should be washed out just before a feed twice daily for several weeks, and thence once daily for several weeks longer, with a solution of sodium bicarbonate (2 grains to the ounce) through a Jacques' soft catheter. This must be continued until not only the vomiting has stopped, but till the weight is steadily increasing.

It must be emphasized, however, that the attitude of physicians on this subject has altered greatly of recent years, and that surgical interference is now regarded as the right procedure, which, indeed, has been strongly advocated by Cautley for a good many years.

The Intestines.

Discharge of Food into the Duodenum.—As has already been pointed out, the pyloric sphincter is controlled by the secretion of HCl. Thus the food is held in the stomach until provision is made for the continuance of gastric secretion, until the gastric juice has had time to act, and until the food can carry with it the acid needed for processes in the duodenum. But as water excites no gastric secretion, it begins to leave the stomach almost as soon as it enters. This quick exit before it is acidified doubtless explains the readiness with which it conveys infection, the acid being antiseptic. The slow discharge of fats from the stomach is explained by the fact that not only do they inhibit secretion there, but when they begin to be digested in the duodenum they give rise to fatty acids which will help to keep the pylorus closed. Consequently, they leave only as fast as they are absorbed by the small, or carried into the large, bowel. They are almost invariably present in the stomach seven hours after ingestion.

The discharge of the gastric contents may be reflexly delayed in another way. Murphy and Cannon found, after high intestinal section and suture, that for almost six hours after recovery from anæsthesia, the pylorus remained tightly closed. There is a remarkable coincidence between the period of delay in the discharge and the time required for the primary cementing of the intestinal wound. This is clearly protective, and

probably explains the spasm and consequent hyperchlorhydria of reflex dyspepsia. It may occur in duodenal ulcer and in diseases of the biliary passages, both of which we know are accompanied by hyperchlorhydria, a common result of pyloric spasm. This occurs also when the colon is irritated, and it has become recognized of late that hyperchlorhydria is an almost invariable accompaniment of colitis, and frequently results from chronic appendicitis.

Movements of the Small Intestine.—These are of two kinds: (1) Pendulum (Bayliss and Starling) or segmentation movements (Cannon) which travel at the rate of 2 to 5 centimetres a second, and depend on muscle tone. They cannot move the contents along, but serve to mix them thoroughly by forming a number of alternately constricted and dilated areas, each of which is divided exactly into two by the next movement. (2) Peristaltic movements, a powerful wave of constriction following immediately on a wave of dilatation, so that the contents are always being driven from a contracted into a dilated area. These waves apparently depend on an intrinsic nervous mechanism of the bowel, the plexus of Auerbach. At the same time the extrinsic nerves affect these waves, the vagus increasing and the splanchnic inhibiting them. An exception to this general statement is the fact that the splanchnic nerve supplies motor fibres to various sphincters. Elliott has formulated the law of the hollow viscous as follows: 'If the quiet lodgment of the contents be facilitated by the presence of sympathetic inhibitory

nerves to the body of the viscus, there will also be sympathetic motor nerves at the sphincter closing the exit.' The pylorus, the ileo-cæcal valve, the internal anal sphincter and the neck of the gall-bladder are all thus supplied.

Extrinsic mechanisms occasionally interfere with the normal intrinsic ones, usually in the direction of inhibition. This is observed after operations. It has been shown that even gentle manipulation of the stomach and intestines produces a much greater post-operative inactivity than anything else in the operation. That this is due to reflex inhibition is proved by the fact that it is overcome for a time by injection of eserine salicylate ($\frac{1}{100}$ grain four hourly for six doses), which diminishes these nervous influences, while tincture of aloes, which is particularly effective in promoting peristalsis in the cat, is quite ineffective after such manipulation of the gut as results in paralysis. Some emotional states are a strong stimulus to peristalsis, while others inhibit it. Thus in most animals any sign of rage or distress or mere anxiety is accompanied by a total cessation of the movements of the stomach. In the dog's intestine, on the other hand, after signs of emotion there is a marked increase of activity lasting for only a few minutes. Emotion as a factor in the production of diarrhœa is well known.

Apart from operative interference or organic obstruction delay seldom occurs in the small intestine. Cannon never observed it experimentally, and Hurst found it only in lead-poisoning. I have occasionally

observed it with X rays. Peristaltic rush, on the other hand, is not infrequent here, and may be the result of a purgative or an enema. Of the three foodstuffs, carbohydrates normally pass the most rapidly. This may be associated with the presence of cellulose and its well-known mechanical action. Cannon noted that normally the peristaltic wave can force the contents past kinks and sharp bends without difficulty, an observation which has an important bearing on Arbuthnot Lane's views of intestinal stasis. Owing to the comparatively dilute condition of the contents of the small bowel the movements of segmentation and peristalsis are not so clearly seen with the X rays as in the stomach and colon. After an ordinary meal the average time for the shadow to appear in the cæcum is four and a half hours (Hurst), so that the rate of progress through the 22½ feet of small intestine is rapid.

Cannon also made some interesting observations on the result of intestinal anastomosis. After an end-to-end union of the intestine there was no evidence of stasis, but after lateral anastomosis there was a more or less complete blocking. In time the tube may be straightened out after a lateral anastomosis, with restitution of functional efficiency, but there is a period when there is a danger of obstruction, because the division of the circular coat of muscle interferes with peristalsis. Further, if the blind ends of the lateral loops are allowed to extend beyond the openings there is a danger of the proximal portion becoming

packed with hardened fæces, and of the distal becoming invaginated until it fills the lumen of the anastomosis.

Movements of the Large Intestine.—Functionally the large intestine can be divided into three portions which do not correspond exactly to the anatomical divisions: (1) a proximal part characterized by the presence of antiperistaltic waves, (2) an intermediate part conforming to the type of movements seen in the small intestine, and (3) a distal portion, the rectum, where the central nervous system again assumes control. It is in this last part that disturbances are most likely to occur because the automatic call for the discharge of its contents can be voluntarily suppressed. Antiperistalsis is rather a misnomer, for it is really a rhythmical series of reversed segmentation movements depending largely on the degree of tension present, and not peristaltic waves originating from a ring of tonic constriction. It serves to churn the food and delay its onward passage. It necessitates a true muscular sphincter at the ileo-cæcal valve, and the development of a cæcum is a corollary to its occurrence. In animals like the rabbit and the herbivora in general, where the cæcum is long, it can be filled only by the aid of antiperistalsis. This also accounts for the fact that the emptying of the cæcum is never complete.

In the large bowel the absorption of water mainly occurs, and as the contents become more solid, the shadow cast on the X-ray screen becomes more intense, so that the segmentation waves and peristalsis become very distinct. The onward progress also

becomes much slower, so that the colon is traversed in about six hours. During the night the movements are considerably slower than this. According to Hurst, the entire large intestine below the splenic flexure is normally evacuated at a single act of defæcation. The action of some purgatives in producing peristaltic rush in the large intestine is marked. Thus senna causes an evacuation as soon as it enters the colon, and anti-peristalsis is completely inhibited. Enemata, on the other hand, have a markedly stimulating action on the antiperistalsis of the colon. Small rectal injections are never forced even partially into the small intestine; but with larger amounts, whether fluid or semi-solid, many coils of the small gut become filled. In cases of cæcal fistula the ileum has been transplanted into the transverse colon without stopping the discharge, for here, as elsewhere in the alimentary canal, the contents will continue to follow the direction of the powerful muscular waves which will be very incomplete where the circular coats have been divided. This has an important bearing on short-circuiting operations designed to exclude the large bowel. If the normal path be left open, much of the contents will continue to pass along it. Lockhart Mummery considers that occlusion of the colon, either partial or complete, is usually incompatible with permanent good health. Accumulation of fæces occurs sooner or later in the occluded loop, and causes trouble which, if unrelieved, produces auto-intoxication and possibly abscess or perforation.

Defæcation.—Approximately nine hours after ingestion material enters the descending colon, and remains there until the next action of the bowels. This means, as Hurst has pointed out, that when the bowels are opened regularly once a day the interval between a meal and the excretion of its residue will vary between nine and thirty-three hours. As the pelvic colon becomes distended it rises, widening the acute angle with the rectum, thus removing an obstacle to the onward progress of the contents. The rectum should normally be empty, except during the act of defæcation, but in constipated persons it always contains some fæces. The first meal of the day evokes peristaltic waves throughout the whole alimentary tract, driving some of the contents of the pelvic colon into the much more sensitive rectum. It is distension of the rectum which evokes the desire to defæcate, which may be produced either by the passage of fæces from above or by a balloon introduced through the anus. The distension may be increased voluntarily by contraction of the abdominal muscles of the walls. A powerful wave of peristalsis is thus produced in the rectum, and the discharge of contents is facilitated by the recto-coccygeus muscle, which draws the rectum backwards, straightening out the angle in its lower portion, while the anal sphincters are relaxed. The levator ani mainly acts as a voluntary sphincter, but it may also help in defæcation by directing the fæces forward towards the entrance to the anal canal, and by drawing this canal upwards over the fæcal mass,

and finally contracting firmly behind it. In multiparous women injury to, and atrophy of, the levator ani play a distinct part in the production of constipation. Again, the levator ani being a voluntary muscle can resist the call to defæcation. When this occurs the desire soon passes off until the arrival of more fæces again distends the rectum. Repetition of this process blunts the sensibility of the rectum until it habitually retains a considerable amount of fæces. Although such a patient is constipated, X-ray examination shows that there may be no delay in the onward passage of the intestinal contents until the rectum is reached. For this type of constipation Hurst has revived the term *dyschezia*, originally used by Robert Barnes to denote painful evacuation of fæces. As he points out, there is little use in treating such a case by aperients which have to act on a colon which is normal in its response. The rational procedure is the routine use of enemata, by which the rectum can be emptied and its tone regained.

In Hirschsprung's disease, often erroneously called a 'congenital idiopathic' dilatation of the colon, the rectum is not involved in the dilatation. The hypertrophy of the muscular coats of the colon shows that atony is not the cause, but that there must primarily be an obstruction. This, according to Hurst, is primarily fæcal, as a rule, though in rare cases it may be spasmodic. Once the colon becomes dilated, it produces a kink by overhanging the undilated part below. The obstruction is thus maintained even when

the impacted fæces originally present have been evacuated. As this obstruction can be seen only when the parts are in position, the failure to discover it *post mortem* is explained, since there is no organic stricture. In the same way it may not be detected at operation, since the laparotomy allows the dilated colon to rise out of the abdominal wound, which relieves the obstruction for the time being. Blochmann urges that there is a valvular obstruction usually produced by a congenital kinking at the junction of the pelvic colon with the rectum. On the view put forward above, the kink is not congenital, but results from constipation in the first instance. In treatment the most important thing is to empty the colon as completely as possible by enemata, and then to prevent its becoming overloaded again by the use of a rectal tube passed above the kink. If this cannot be done a laparotomy will allow of the distended colon being pulled upwards, and the tube can be passed. Strychnine and abdominal massage are valuable adjuncts to treatment. The radical operation of removal of the colon is fraught with grave danger to life. Hurst advises its performance in three stages: First, a colostomy; secondly, an anastomosis between the ileum and the undistended rectum; and finally, a colectomy, if necessary. In any case, the prognosis is unfavourable once the condition is thoroughly established.

Intestinal Stasis and its Consequences.—A new interest has been aroused in the mechanical factors in digestion by Sir Arbuthnot Lane's work on viscerop-

tosis and intestinal stasis. The very enthusiasm with which he has advocated his views has perhaps tended to excite opposition. However, considerable evidence has now been accumulated by independent observers, who were sceptical at first. Probably while the more extreme parts of his doctrine will not command assent, his main contention will gain increasing support. He holds that the main cause of visceroptosis is the adoption of the erect posture, while contributory factors are the stretching of muscles and the relaxation of ligaments due to repeated pregnancies, tight lacing by wrongly constructed corsets, lifting of heavy weights, emaciation, and muscular debility. He also attaches considerable importance to the customary sitting posture adopted during defæcation by civilized races as contrasted with the primitive squatting attitude, as helping to force the viscera down into the pelvis. It will be noted that many of these causes are more operative in women, in whom the condition is much commoner than in men, where the lesser obliquity of the pelvic brim also affords more support to the viscera. The three principal results of this visceroptosis are, according to Lane, (1) the formation of conservative adhesions along the lines of resistance to downward displacement, (2) the consequent production of kinks along the course of the gastro-intestinal tract, leading to (3) stasis, with delayed digestion, constipation, and auto-intoxication.

The *adhesions* are not the result of inflammation, but are developed where the mesenteric attachment has

been dragged upon to counteract the dropping of the viscera. The existence of such adhesions has long been known, but the interpretation is new. They may occur (1) between the pylorus and the under surface of the liver in front of its transverse fissure, extending along the cystic duct and gall-bladder; (2) between the outer aspect of the cæcum and the adjacent abdominal wall; (3) between the hepatic flexure and the right kidney; (4) between the descending colon and the abdominal wall; (5) fixing the sigmoid loop of the pelvic colon to the brim of the true pelvis. On the other hand, the splenic flexure is naturally well supported by the costo-colic ligament, which may become thickened as the downward drag increases.

The *kinks* may form (1) at the pylorus in consequence of the first of the adhesions described above, causing delay in the emptying of the stomach; (2) at the junction of the duodenum with the jejunum, resulting from the end of the duodenum being firmly fixed by a peritoneal band, while the freely mobile jejunum drops; (3) at the ileo-cæcal junction due to prolapse of the cæcum into the pelvis while the ileum is held up by a thickened layer of mesentery; (4) at the appendix by an acquired mesentery, which leads to the distal part being sharply flexed on the proximal part; (5) at either end of the transverse colon by adhesions to the right kidney at one end, and by the costo-colic ligament at the other, while the gut in between drops; and (6) in the pelvic colon, where it becomes adherent to the brim of the true pelvis.

A large number of symptoms have been referred by

Lane and his followers to intestinal stasis—a poor appetite and a bad taste, offensive breath, flatulence, constipation, attacks of nausea and vomiting, and frequently abdominal pain with points which are tender to pressure. The general effects of the intoxication are seen in the depression and want of energy, both mental and physical. The circulation is impaired, the hands and feet are cold, clammy, and often livid, the skin loose and inelastic, becoming pigmented. Progressive emaciation, headache, backache, muscular pains and aching joints are not uncommon. In women the breasts show the changes of chronic mastitis, and often undergo cystic degeneration. Without going into the more remote effects assigned to this cause, which, starting with diminished resistance to tuberculous infections, threaten to extend until every ailment and lesion are thus explained, we may note the ingenious way in which the theory is made to account for many diseases of the alimentary tract and its annexes. The mechanical retention of stomach contents causes them to become more acid, from continued secretion, which may be a potent cause of erosion and ulceration of the gastric mucosa. The mucous membrane of the 'kinked' duodenum becomes congested and then ulcerated. On this view gastro-jejunostomy is not a rational treatment for duodenal ulcer, and Lane holds that it benefits only by anchoring the mobile jejunum in such a way that it cannot kink upon the fixed duodenum. In many cases the kink is slight enough to be got over by lying down after meals. Duodenal ulcer can often be treated successfully by

rest and medical means, and the absolute rest necessitated by the operation no doubt plays an important part in the good results attributed to it. Ascending infections of ducts can occur more readily when as a result of stasis bacteria normally confined to the large intestine ascend into the ileum, and so gall-stones and pancreatitis are explained. As has been already said, Lane holds that adhesions round the appendix are more frequently the cause than the result of appendicitis. Mucous colitis is referred to similar causes, and carcinoma of the intestines is held to result from irritation due to material passing along the various kinks and flexures.

Such sweeping conclusions have naturally aroused opposition. It must be remembered that Cannon found that peristalsis was able to drive on the contents of the bowel past quite sharp kinks, and in tuberculous peritonitis, or malignant disease of the intestines kinks are formed which in many cases produce neither constipation nor stasis. There is a muscular sphincter of some length at the ileo-cæcal valve, which might easily produce the appearance of a narrowing by adhesions, and similar sphincters have been described by Keith in the position of most of Lane's kinks. As the bismuth shadow is often seen to be as intense on the distal as on the proximal side of the 'kink,' it cannot always mean a definite obstruction. Again, in healthy persons, the transverse colon may be quite as low as in cases of visceroptosis, without any symptoms. But when a number of observers agree that they can recognize the condition by its symptoms, that it can be confirmed by X-ray examina-

tion and subsequently at the operation, and that it can be cured by short-circuiting, and that the patients remain cured, it is hard to see what further proof can be demanded. That extravagant claims are being made does not disprove the main contention. The radiographic evidence adduced by A. C. Jordan in support of Arbuthnot Lane's views cannot be lightly brushed aside. At the same time we must remember that sympathetic irritation of the bowel would inhibit peristalsis and contract sphincters. Therefore emotional causes might produce intestinal stasis.

Treatment of Visceroptosis.—Prophylactic measures include the inculcation of regular habits as to the bowels, starting in childhood and continued throughout life, the use of low lavatory seats, or of footstools high enough to allow of a squatting posture during defæcation, not lifting heavy weights or getting up too soon after debilitating illnesses and confinements, the avoidance of corsets exerting a downward pressure, and the correction of a tendency towards emaciation. Besides the ordinary measures for the relief of constipation special mention must be made of liquid paraffin, which has lately acquired such a vogue in the treatment of constipation. Not being absorbed, it increases the bulk of the fæces, and really does seem to facilitate the onward progress of the intestinal contents. The drawback to its use is that in some cases it produces a slight degree of incontinence; but this is generally because too large an amount has been taken. I therefore start by prescribing quite a small dose, such as a drachm, and increasing slowly till the quantity

suitable for the individual has been found, which may be an ounce or more. Some preparation of Iceland moss, such as regulin, prescribed at breakfast time with some cream, by its power of absorbing water and swelling up, is useful occasionally to increase the bulk of hard dry fæces; but I have not found it as effective as paraffin, while other observers have sometimes found it to cause troublesome accumulations in the cæcum. Abdominal massage and exercises designed to develop the abdominal muscles may be helpful, though in some of the worst cases of ptosis the abdominal walls are quite good, the movement of the viscera being downward and not forward. A well-fitting abdominal support, of which I believe the best to be Curtis's, is often of great assistance. It might be thought that such a support can only do good, and should only be worn when the abdominal muscles are so weak that they are unlikely to recover. Such, however, is not my experience, and Hurst believes that the good effect of the support is due to its increasing the intra-abdominal pressure rather than to its replacing any particular viscus. He regards a disturbance of the balance between the thoracic and abdominal pressures as one of the main factors in inducing visceroptosis, and thinks that if the drag on the viscera is prevented, the patient is enabled to eat more without fear of discomfort, and to take more exercise, thus helping to overcome the sluggish action of the intestines. If all these points are carefully attended to, surgical interference will not often be required. When the X rays show pyloric spasm and

delay chiefly, or solely, at the cæcum, I think the appendix is generally responsible for the symptoms, and its removal may be indicated.

As to other operative measures, only in exceptional cases is the mere division of constricting bands to be advised. If divided they are apt to recur, and, as has been already pointed out, their formation is compensatory. Such a drastic operation as resection of the whole of the large bowel is certainly to be avoided if possible. Nevertheless, good results have been recorded. Ill results are more likely to escape being placed on record.

W. E. Miles has put forward another view as to the production of intestinal stasis in women, in whom, of course, the symptoms are much more common. As a result of the general sliding down of the posterior wall of the peritoneum, there is a proptosis of the broad ligaments. On the left side this tends to obstruct the pelvic colon where it passes over the shelf formed by the ligament which has assumed a horizontal instead of a vertical position. Adhesions form and still further add to the obstruction. Miles believes that if this obstruction is removed by obliteration of the left broad ligament, the rest of the alimentary canal will recover its tone. That there is a demonstrable pelvic shelf in these cases is certain, but it is not claimed that its mere rectification will cure, since he adds that 'it is essential that a course of intestinal lavage, combined with the daily use of suitable aperients, should be persisted with for several months afterwards.' He

perhaps attributes an excessive share of the improvement to the operation. Waugh has advocated the operation of colopexy, or stitching up of the dropped ascending colon, which he believes to be the main seat of the trouble. I have been much impressed by the frequency with which the focus of an organic dyspepsia is situated on the right side, and also with the co-existence of several such lesions, such as cholecystitis with appendicitis, appendicitis with peptic ulcer, and so on. But I am not satisfied that colopexy is always a remedy, and I have seen great trouble with the consequent adhesions.

Some scepticism is natural when one recalls the number and variety of the surgical short cuts to health that have been advocated, and the disillusion that has too frequently followed. Appendicectomy, gastrojejunostomy, colopexy, intestinal short circuits, and rectification of the pelvic shelf may all have their use in suitable cases. There has been, however, a regrettable tendency of the advocates of each to regard their particular method as a panacea to the exclusion of all the others. This is part of a generally uncritical attitude seen too frequently in the profession, and one that has been satirized by the observant layman. Only by a close and accurate study of the normal mechanism of the alimentary canal can we arrive at sound conclusions as to the value and limitations of any procedure, medical or surgical.

CHAPTER IV

THE WORK OF THE PANCREAS

ALTHOUGH the pancreas provides the most active digestive secretion in the body, and plays an important part in general metabolism, until recently disease in it was not often recognized during life. A consideration of the way in which the pancreas does its work may enable us to realize the difficulties attending this recognition, and the steps by which they are being overcome.

As soon as the acid chyme enters the duodenum the secretion of pancreatic juice begins. Its alkalinity corresponds almost exactly to the acidity of the gastric juice, so that, allowing for the alkaline bile, the total bulk of pancreatic secretion will be rather less than that of the gastric secretion.

Von Mering has shown that injection of acid into the duodenum leads to closure of the pyloric orifice. Not until this acid has been neutralized by the pancreatic juice it has produced can more of the acid contents of the stomach pass through the pyloric sphincter. The secretion is thus exactly regulated to the amount of food arriving from the stomach.

Pavloff thought that the acidity of the chyme

acted by stimulating special nerve-endings in the duodenum, but Wertheimer showed that the acid was equally effective after section of all the nerves in the neighbourhood, or even after extirpation of the solar plexus. The acid produced less effect the further down the intestine it was introduced, until within two feet of the ileo-cæcal valve it ceased to have any effect at all. This paved the way for Bayliss and Starling's important discovery that the hydrochloric acid of gastric juice, when it comes into contact with the mucous membrane of the intestine, leads to the production of a chemical stimulant, *secretin*, which is absorbed from the cells by the blood-stream and carried to the pancreas, where it acts as a specific stimulant to secretion.

Dilute hydrochloric acid was placed in a loop of jejunum which had been previously isolated from the rest of the body except for its blood-supply. The absorption of acid was accompanied by a secretion of pancreatic juice. If, however, the acid were injected direct into the blood-stream, it was ineffective. On the other hand, a saline extract of the intestinal mucosa treated with hydrochloric acid and injected into the blood-stream produced an active secretion. Thus, for pancreatic secretion to occur normally, hydrochloric acid must descend from the stomach, which will only happen in the presence of food.

For some years after this discovery it was generally believed that this chemical mechanism is sufficient to account for all the facts of pancreatic secretion.

Clayton-Greene has, however, recorded a case which seemed to point to nervous influence. During pylorectomy for malignant disease of the stomach a pancreatic fistula was accidentally formed. A few seconds after food was swallowed pancreatic juice began to appear, and this occurred even when the food had only been seen and not swallowed. Nervous mechanisms are distinguished from chemical by their speed, and here the reaction was very rapid.

In 1911 Cathcart obtained pancreatic secretion in animals by vagal stimulation; so that, while the main stimulus is chemical, we must admit a nervous factor as well. It may be safely asserted that after severance of all nervous ties secretin can produce a copious flow of pancreatic juice. Comprehension of this chemical factor brings the regulation of pancreatic digestion more under our control.

Inadequate pancreatic secretion appears to have a striking effect upon growth. Byrom Bramwell has described a condition of persistent infantilism due to this in a lad of eighteen, who did not look more than eleven. He was perfectly formed, bright, and intelligent. His height was 4 feet 4 inches, and his weight 4 stone 7½ pounds. He had suffered from diarrhœa for nine years. The abdomen was swollen and tympanitic. Skiagrams showed that the epiphyses, which should have united between sixteen and eighteen, had not done so. There was no glycosuria. The pancreatic secretion was found to be defective or absent by tests described later. Marked improvement

followed treatment by a glycerine extract of the pancreas. The diarrhœa greatly diminished; he grew $5\frac{3}{8}$ inches in two years, and increased 1 stone 8 pounds in weight, although previously he had not grown for eight years. Signs of puberty, till then entirely lacking, now developed.

Here profound disturbances resulted from pancreatic inadequacy, yet there was no glycosuria, suggesting that it was only the external secretion of the pancreas, and not the internal secretion, that was at fault. I have seen a case of severe congenital syphilis in a boy of sixteen, combined with persistent infantile features. In appearance he looked about eight or ten years old, and all signs of puberty were lacking. Now, congenital syphilis is known to lead to arrested bodily development, but the special feature of interest here was the existence of fatty diarrhœa, suggesting pancreatic inadequacy. There was no glycosuria. At the post-mortem examination the condition of the pancreas typical of congenital syphilis was found. The condition closely resembles, however, the infantilism described by Herter as due to a chronic intestinal infection characterized by an overgrowth and persistence of the flora of the nursling period. And, after all, any chronic disease in early life, which interferes with sufficiently important functions, may be responsible for persistent infantilism.

Why does not the pancreas digest itself? It was long a problem why the digestive organs, themselves composed of protein tissues, should resist digestion by their own ferments. In the case of the stomach, the fact that the

juice only acts in an acid medium, while the blood is alkaline, was held to explain the difficulty. But this only made the case of the pancreas all the more striking. Now, however, we are provided with a satisfactory answer to the riddle. The tryptic activity of the pancreas is hedged around with some remarkable safeguards.

1. *Active trypsin is normally liberated only in the presence of food.* As stated, hydrochloric acid is the stimulant to pancreatic secretion, and this will pass into the duodenum only as the result of food leaving the stomach.

Moreover, fresh pancreatic juice contains inactive trypsinogen. Before this can become active trypsin, it must be acted upon by another ferment, *enterokinase*, which appears to be present only in the succus entericus. Therefore the fluid present in the duct of Wirsung cannot injure the gland, for it is inactive until discharged from the papilla. And although any mechanical irritation of the intestine will lead to the outpouring of mucus, true succus entericus is secreted only in the neighbourhood of the food; while, according to Pavloff, its richness in enterokinase depends on the stimulating action of the pancreatic juice. Whatever the exact stimulus to succus entericus may be, it is difficult to extract enterokinase from the intestine of a fasting animal, so that its presence seems to be dependent on the food. This 'double locking' insures that under normal conditions active trypsin can be liberated only in the presence of food.

The importance of these safeguards is seen on injesting secretin into fasting dogs. Then active pan-

creatic juice is set free, and the intestinal walls are extensively digested.

2. *Trypsin is an unstable body, and rapidly destroys itself, if proteins or their products are not present.* In this way trypsin left over at the end of digestion is soon disposed of.

3. *The blood-serum contains an antibody to trypsin,* thus destroying any ferment which may accidentally enter the circulation.

Trypsin is no exception to the general rule that the introduction of a substance of the protein class into the circulation excites the formation of the appropriate antibody. It is interesting that intestinal worms also contain an antitrypsin. This explains at once their power of living in the intestine and the voracious appetite of their host, who is thus largely incapacitated from assimilating proteins.

For these reasons it is difficult to understand how pancreatic hæmorrhage or necrosis can be due to self-digestion of the gland by trypsin. But probably other things besides enterokinase may be capable of activating trypsinogen. After all, a ferment merely carries out with great velocity, and at the temperature of the body, a reaction which can be performed, though much less readily, by other means.

Delezenne claims that calcium salts can activate trypsinogen, as we know they do fibrin ferment. A pre-existent pancreatic catarrh might lead to the formation of active trypsin within the ducts of the gland; pancreatic calculi, for instance, are rich in

calcium salts. Guleke has advanced evidence that self-digestion by trypsin is the cause of the toxic symptoms in acute necrosis of the pancreas.

Laparotomy for a ruptured pancreas has been followed by rapid digestion of the rectus abdominis in the neighbourhood of the wound. As no injury to the duodenum was found at the necropsy, there could hardly have been activation by enterokinase. The drainage of pancreatic cysts, too, has occasionally been followed by extensive self-digestion along the track of the fluid.

But such cases are exceptional, and the usual cause of the necrosis is probably the passage of infected bile back along the pancreatic duct. As normal bile will not activate trypsinogen, the effect is probably due to some septic infection of the bile. Drainage of the gall-bladder, so as to prevent infected bile from coming into contact with the inflamed tissues has been strongly recommended by Mayo Robson for inflammatory conditions of the pancreas.

Fat Necrosis.

With regard to steapsin the case is different; should the juice be extravasated from the gland, digestion of the body-fat will follow. 'Fat necrosis' is due to this splitting of the body-fat into glycerine and fatty acid, the latter combining with lime salts. Flexner has demonstrated the presence of steapsin in the affected areas, while Opie was able to show its presence in the urine in one such case by its decomposing action on ethyl butyrate.

These opaque white areas, often surrounded by a ring of inflammation, are usually most abundant in the neighbourhood of the pancreas and omentum, which suggests that they are caused by direct extravasation of the steapsin.

Cammidge's 'pancreatic reaction' is founded on the belief that there is a large proportion of a pentose-yielding substance in the pancreas, so that in disintegration of the gland we might expect to find it in the urine. But it does not appear to have met with general acceptance.

Other Pancreatic Ferments.

Pancreatic juice can act on all three classes of food-stuffs. The starch-splitting ferment, amylopsin, only differs from ptyalin in saliva in being more rapid and in being able to act on unboiled starch. Were amylopsin to enter the circulation, it could do no harm beyond digesting the glycogen in the liver. This could not account for pancreatic diabetes, since the glycosuria does not cease with the emptying of the glycogen reservoirs, and is most intense after total excision of the pancreas.

Pancreatic juice also contains small amounts of erepsin, which completes the digestion of proteins, a milk-curdling ferment, and a malt-sugar-splitting ferment. But they are of subsidiary importance here, being more abundantly present in other digestive secretions.

The Influence of the Pancreas on General Metabolism.

Since the classical experiments of von Mering and Minkowski, much interest has been taken in the relationship of the pancreas to diabetes. Extirpation of the pancreas in dogs is followed within twenty-four hours by glycosuria, reaching its maximum on the third day, when it amounts to 8 or 10 per cent. on a carbohydrate-free diet. This is associated with excess of sugar in the blood, and the presence of acetone in the urine. The constancy of the ratio of the carbon to the nitrogen excreted (2·8 to 1) is best explained by supposing that protein is the source of this sugar. In repeating these experiments Allen found that severe diabetes regularly occurred when nine-tenths of the gland were removed and frequently when less was taken away.

The fact that an adequate pancreatic remnant could still exert its control, even if its connection with the duodenum were severed, naturally suggested that the pancreas furnished an internal secretion which promoted the utilization of sugar. The cell-islets of Langerhans were thought to form it. These are ovoid groups of poorly staining cells of two kinds, called alpha and beta, which appear to arise from the secreting alveoli, but to lose their connection with them.

Normally they contain no ducts, and are supplied with wide tortuous capillaries or 'sinusoids.' In man they are scattered irregularly through the gland, though in some animals, such as the cat, they are constantly

in the centre of the lobe. Rennie found very large islets in the bony fishes, including in some a principal islet, separated from the rest of the organ, visible to the naked eye, and capable of dissection.

Opie strongly supported the view that injury to these islets is responsible for the disturbance of carbohydrate metabolism. He claimed that the more selective the influence of a lesion is upon the islets, the more likely is it to cause glycosuria. Thus interstitial pancreatitis may be interlobular or interacinar; the latter soon affects the islets which lie deep within the lobules, whereas the former has to be far advanced for the islets to become involved. It is the interacinar form which is more likely to be associated with glycosuria. Allen regards hydropic degeneration of the cell-islets to be a specific diabetic phenomenon, produced by overtaxing their weakened assimilative power. Only the beta cells seem to be concerned in this.

It has long been known that if the pancreatic duct be tied, the alveolar cells degenerate, but the cell-islets remain. Yet it was reserved for Banting to apply this as a method of obtaining the internal secretion which others had repeatedly failed to isolate. Having extracted by this means an active preparation to which the name *insulin* was given, it was soon found possible to obtain it by fractional alcoholic precipitation from the intact pancreas. It appears to be a substance of a larger molecular weight than other hormones, and can be obtained from other sources including yeast (Winter and Smith). Its practical importance is dealt

with in the chapter on Glycosuria. Here it is sufficient to say that the formation by the cell-islets of an active internal secretion influencing carbohydrate metabolism and reducing blood sugar has at last been proved up to the hilt.

The Manifestations of Pancreatic Disease.

Disease of the pancreas is still considered to be rare, but, in view of its multifarious duties, it would be strange were this really true. Gross lesions may be rare, but inflammatory changes are not uncommon. 'Catarrhal jaundice' is probably pancreatic in origin sometimes, and it is possible that in many cases of intractable dyspepsia the pancreas is at fault.

Three main factors tend to obscure the diagnosis of pancreatic disease:

1. 'Disease of the organ is seldom uncomplicated, but is usually consequent on changes in the duodenum, liver, or bile-passages' (Opie); and when not the result of such changes, it may be the cause of them.

2. The digestive work of the pancreas can be largely carried out by other secretions. Digestion of fat has been thought to be an exception to this statement. But even under aseptic conditions the gastric juice is capable of splitting 50 to 60 per cent. of the fat of the food into fatty acid and glycerine. Moreover, fat-splitting can also be accomplished by intestinal bacteria. This accounts for Abelmann's observation that, after excision of the pancreas in dogs, 58 per cent. of

the fat of milk is still digested, and for Hédon's and Ville's, who found that 50 per cent. of fat was digested after the pancreatic juice was prevented from reaching the intestine.

Another source of fallacy is that occlusion of the main pancreatic duct may be partially compensated for by the duct of Santorini.

On the other hand, occlusion of the bile-duct, or tuberculosis of the alimentary tract, may result in excess of fat in the stools without pancreatic disease.

8. Pancreatic disease is only one of many causes of glycosuria, and lesions which only affect part of the gland may not be accompanied by glycosuria at all.

Bearing these sources of error in mind, we may now consider—

The Signs of Pancreatic Inadequacy.

1. *Defective External Secretion* as indicated by—

(*a*) *Failure of Tryptic Digestion.*—Unaltered muscle nuclei may be found in the fæces after a meat meal.

To aid the detection of these nuclei, the muscle fibres may be enclosed in small silk or muslin bags. Schmidt and Kashiwado employ capsules containing lycopodium and stained muscle nuclei, the large size of the lycopodium grains acting as a guide to the coloured nuclei. Even with this aid the finding of the nuclei is not an easy matter. Sahli's method of enclosing iodine in gelatin capsules hardened by formalin cannot be recommended. He claims that if the pancreatic

secretion is inadequate the capsule will not be digested and therefore the iodine will not pass into the urine or saliva. But if the capsules are not hardened enough, they may be digested in the stomach; while if they are hardened too much, as is more commonly the case, no reaction is obtained even though the pancreas is healthy, because the capsule now resists tryptic digestion also.

It is claimed that trypsin can be demonstrated in normal stools by placing a small quantity of fæces on a gelatin plate, when a small area of digestion will result. With absence of the pancreatic secretion this would not occur.

(*b*) *Failure of Starch Digestion.*—Though ptyalin can digest boiled starch, amylopsin alone can digest unboiled starch grains. Abelmann found 20 to 40 per cent. of the starch in the fæces after experimental excision of the pancreas. Chronic pancreatitis may cause oxaluria from intestinal fermentation of carbohydrates (Cammidge and Robson).

(*c*) *Failure of Fat Digestion.*—This may result in true steatorrhœa, or in the presence of fat droplets, fatty acid crystals, or soap in the fæces in such amounts as can only be detected by the microscope. But a quantitative estimation is necessary to determine the excess of fat satisfactorily. In normal fæces the saponified and unsaponified fats are approximately equal in amount, the total amount of the two being 15 to 25 per cent. of the solid matter. As the pancreas provides for the fat-splitting that must precede saponification,

unsaponified fat will be in excess of the saponified if the excess of fat in the stools is due to a pancreatic defect. On the other hand, the bile-salts provide for the absorption of the fat already digested by the pancreatic juice, so that if the excess of fat be due to loss of bile simply, the saponified fats and free fatty acids will be in excess, because they cannot be adequately absorbed.

2. *Defective Internal Secretion* as indicated by—

(*a*) *Diminished Sugar Tolerance.*—Though spontaneous glycosuria may be absent in pancreatic disease, it may often be excited by a carbohydrate diet. Thus, Wille tested a large number of patients with various diseases by administering 70 to 100 grammes of dextrose dissolved in ½ litre of tea or coffee. The urine was passed just before, and was then tested at intervals of two hours. If alimentary glycosuria exists, sugar should be found two hours after a meal. A normal person can take 150 to 200 grammes of dextrose at one time before glycosuria occurs.

Wille found that, of fifteen cases of alimentary glycosuria thus tested, which he was able to follow to necropsy, ten had grave lesions of the pancreas. Though alimentary glycosuria may occur in other conditions, such as exophthalmic goitre and alcoholism, it remains a sign of considerable value when in conjunction with other evidence of pancreatic insufficiency. Owing to changes in the renal threshold, there may be hyperglycæmia without glycosuria. As explained in the chapter on Glycosuria, examination

of the blood therefore provides more satisfactory evidence than examination of the urine. Glycosuria may be rather a late symptom, and one that makes the prognosis more serious.

(b) *Adrenalin Eye Test.*—When adrenalin is instilled into an excised eye, the pupil dilates. But normally this mydriasis does not occur with the eye *in situ*. If, however, the pancreas is inadequate, the pupil will dilate in from twenty minutes to one hour after one drop of the liquor adrenalin hydrochlor. is dropped into the eye, and another drop five minutes later. Loewi explained this as due to an upset in the normal antagonistic action of the suprarenals and the pancreas. If the latter is in defect, the former will be relatively in excess, and the addition of adrenalin will enable it to assert itself, so that dilatation of the pupil is no longer inhibited. The dilatation is often an eccentric one. The test may fail if repeated within a week. My experience of the test is that it is, if anything, too sensitive. The primary disease may be in the liver, for example, and the pancreas merely secondarily involved, yet the reaction is positive. I had an example of this in a primary carcinoma of the liver with a slight secondary pancreatitis, and I have seen a positive reaction in acute appendicitis. Again, if there is thyroid excess, the reaction may be positive, although there is no disease of the pancreas, for there is also an antagonism between the internal secretions of the thyroid and pancreas. The test is simple and easily applied, but too much reliance must not be placed on it.

(c) *Increase in Urinary Diastase.*—There is normally

a diastatic ferment in the urine, and it is found to be much increased in recent pancreatic diseases. Indeed, at St. Bartholomew's Hospital we have come to regard it as one of the best of the pancreatic tests. Ten test-tubes are taken containing amounts of urine varying from 0·6 to 0·06 c.c. The smaller quantities are measured by using a 1 in 10 dilution. The amount of fluid is made up to 1 c.c. by the addition of 1 per cent. NaCl. Two c.c. of a 0·1 per cent. starch solution is added to each tube, and the contents carefully shaken. The tubes are kept in a water-bath at 38° C. for half an hour, and then placed in cold water for two or three minutes to stop the ferment action. To each tube is added 1 drop of a 1 in 50 normal solution of iodine in distilled water, and the first tube in which a blue colour appears is noted. Here there must be some undigested starch, while in the one below in the series the digestion is complete. Thus, if the tube containing 0·1 c.c. of urine is the first to show blue, in the one containing 0·2 c.c. digestion is complete—*i.e.*, 0·2 c.c. will digest 2 c.c. of 0·1 per cent. starch solution in half an hour, and 1 c.c. will therefore digest 10 c.c. We accordingly say that this urine contains 10 units. The normal figures average 10 to 20 units, but may range between 6·6 and 33·3 units. The test was originally designed by Wohlgemuth as a measure of renal efficiency, the output being lowered if this were impaired. But subsequent work has shown that the diastase in the urine does not necessarily run parallel with the diastase in the blood, which is perhaps what we might expect from what we know of the behaviour of the kidney

threshold towards substances useful to the body. The test has proved of more value in the recognition of pancreatic disease, because here the alteration of the amount in the blood is so gross that the renal threshold is, as it were, flooded. In acute pancreatitis one might find 300 to 500 units—in one case of mine 1,000 were present—while in less acute cases 50 to 100 units may be found. In very chronic conditions there may be no excess, but even a deficiency. In ordinary clinical diabetes a low value is the rule. It was at first assumed that this diastase was merely pancreatic amylopsin reabsorbed into the blood stream, and was evidence of some obstruction to the pancreatic ducts, though in that case it would not be easy to explain its presence in normal urine. But Cammidge, with Forsyth and Howard, has adduced cogent reasons for believing this diastase is hepatic in origin. The diastase value rises as more and more of an animal's pancreas is excised, right up to total extirpation. As it is clearly impossible for a non-existent gland to produce an enzyme, diastase cannot come from the pancreas. On the other hand, hydrazine phosphate, which has a toxic effect on the liver but not on the pancreas, reduces and may completely abolish the diastase output. These authors conclude that diastase is the agent which converts glycogen into sugar, and that its action is controlled by the internal secretion of the pancreas. If such control fails there is for a time a greatly increased production of diastase by the liver, though this may not by itself produce glycosuria.

3. *Signs of Pancreatic Disintegration.*—Cammidge's

pancreatic test would come under this head, as the source of the pentose in the urine is thought to be the pancreatic cells breaking down as the result of inflammatory change. But, as already stated, most observers have concluded against the value of this test, although the presence of this pentose can certainly be occasionally demonstrated.

Other evidences of pancreatic disease may be obtained from—

4. *Pressure Symptoms.*—These may be referred to—

(*a*) *The Common Bile-Duct, producing Jaundice.*—In new growth of the pancreas the obstruction may be complete, while in gall-stones it is more likely to be incomplete, so that stercobilin can be extracted from the fæces by acid alcohol or amyl alcohol, even though they appear quite clay-coloured. The extract gives a band in the blue on spectroscopic examination, and a green fluorescence with zinc chloride and ammonia if there is any stercobilin present.

(*b*) *The Portal Vein, producing Symptoms of Portal Obstruction.*—This is very uncommon.

5. *Nervous Symptoms, from Irritation of the Solar Plexus.*—In acute pancreatic diseases, such as hæmorrhage, the pain is very severe, the patient feeling as if he were gripped in a vice. Vomiting, meteorism, and collapse follow. In subacute cases there may be periodic seizures of pain and vomiting, like the gastric crises of tabes.

We may say that if the adrenalin eye test and the diastase test are negative, it is seldom worth while to undertake more elaborate investigations. If there

are fatty stools without jaundice, and the excess of fat is in the unsaponified form, it is very suggestive of pancreatic disease. If there are also muscle nuclei in the stools, it strengthens the diagnosis. If all these symptoms are present in addition to glycosuria, the diagnosis is almost certain.

General Principles of Treatment in Pancreatic Disease.

Certain considerations govern the treatment of pancreatic diseases in general, which may be discussed here without describing the treatment of particular diseases of the organ.

1. *Dietetic Treatment.*—Pancreatic juice contains ferments which are capable of acting on all foodstuffs, and the only one able to split fat to any extent, the lipolytic power of gastric juice not being of much practical importance. It therefore follows that when the pancreas is diseased, fats are badly borne, for not only are they wasted, excess of unsaponified fat appearing in the stools, but by coating over the proteins they hinder their absorption and increase their putrefaction. Proteins are digested by pepsin, and can therefore be given so long as a form is chosen in which they can be acted upon rapidly in the stomach, such as minced meat. Certain proteins like caseinogen are also digested by the erepsin of the succus entericus, and can therefore be used—*e.g.*, plasmon but

not egg-albumen. In addition, the relatively large amount of sulphur contained in eggs renders them very prone to putrefactive changes. Gelatin, on the other hand, does not contain aromatic bodies, and so is not so liable to these changes, and can replace proteins to a limited extent.

For the digestion of starch we have to rely upon the ptyalin of the saliva; and to take advantage of this, starchy foods should not be given in a soft form, such as ground rice, but in a dry, crisp form, like toast, biscuit, or rusk, which, requiring thorough mastication and insalivation, reaches the duodenum already largely digested. Sugars like glucose can be absorbed without further digestion, while cane sugar, maltose, and lactose can be digested by the succus entericus. But their use in pancreatic diseases is, unfortunately, limited by the diminished sugar tolerance found in many pancreatic lesions. The limit of carbohydrate tolerance should therefore be determined in the way described under Diabetes. If glycosuria is already present, the ordinary dietetic rules for that condition apply.

2. *Regulation of the Pancreatic Secretion.*—The acid of the gastric juice is the great stimulant to both the internal and the external secretion of the pancreas. Accordingly, if it is deficient, it should be reinforced by the administration of dilute hydrochloric acid, or better, 15-grain tablets of betain chloride (sold as oxyntin or acidol), freshly dissolved in water after meals. This

liberates nascent hydrochloric acid slowly in the stomach. On the other hand, hyperchlorhydria over-stimulates and finally exhausts the pancreas, thus helping to set up chronic pancreatitis. It should therefore be corrected by alkalies, including magnesia, after meals.

8. *Supply of Deficient Ferments.*—This presents difficulties. The simplest method would be to pancreatize the food before administration, but this is liable to impart a bitter, disagreeable flavour. If ferments are given to act when the duodenum is reached, they will be destroyed in the stomach unless enclosed in capsules capable of resisting gastric digestion, and then we can feel little certainty that they will be set free in the duodenum. Keratin-coated capsules are supposed to be the best. Capsules of gelatin toughened in formalin are apt to escape undigested even in the healthy subject. Taka-diastase has been given before meals for the digestion of carbohydrates. One or more $\frac{1}{4}$-grain tablets of Pankreon with meals may be given a trial. Holadin is said to contain all the external and internal secretions of the gland. As it has been repeatedly demonstrated that the internal secretion of the pancreas cannot be absorbed by the intestinal mucosa, the advantage of its addition is problematical. It is given in capsules. Stockton states that he has been unable to convince himself that any such ferments produce any improvement in the general condition of the patient or in the stools. He adds that many preparations on the market are practically inert, and many

combinations are self-destructive, provided they are made as described.

4. *Disinfection of the Pancreatic Ducts.*—Two drugs are known to be excreted by the pancreatic ducts, as well as by other channels. These are helmitol and aspirin, both of them disinfectant in action. Routine employment of them in doses of 5 to 10 grains three times a day is therefore a rational procedure, and should be given a thorough trial. But perhaps the most efficient means of ridding the pancreatic ducts of infection is to drain them by a cholecystostomy, which, if indicated, should not be too long delayed.

5. *Diminution of Intestinal Putrefaction, resulting from Diminution or Absence of the Pancreatic Juice.*—The dietetic factors in this have already been considered, and the question of intestinal antiseptics is discussed in a later chapter.

Any chronic disease of the pancreas, accompanied by insufficiency of its secretion, will call for some or all of these methods of treatment.

CHAPTER V

THE WORK OF THE LIVER

For a long time the discrepancy between the great size of the liver and the meagre amount of its external secretion, the bile, proved a puzzle. Gradually it was realized that this secretion only represented a small part of its activities. In several respects it shares its duties with the pancreas and the spleen.

The liver and pancreas are both developed as outgrowths of the alimentary tract, and their ducts are innervated in the same general way as the canal from which they develop. Their close co-operation is further shown in the way they pour their secretions into the alimentary tract at the same point, in their complementary rôles in the utilization of fat and in carbohydrate metabolism, as well as by the circulatory conditions which insure that any internal secretion from the pancreas shall pass straight to the liver. Situated on the path by which all the blood from the digestive organs enters the systemic circulation, it is not surprising to find that the liver helps to prepare *all three foodstuffs for utilization by the tissues. The bile it forms is at once an excretion and a secretion.* But further, the liver is an important agent in detoxication and in maintaining the constant composition of

the blood. Just as on the metabolic side it co-operates with the pancreas, so on the hæmolytic side it co-operates with the spleen.

Of late a number of tests have been designed to estimate the functional efficiency of the liver. The earlier and simpler attempts failed because its great reserve capacity was not realized. For, like the heart, lungs, and the kidneys, the liver does not normally exert its full activity, and so does not reveal its failure of function to ordinary tests until this has fallen to so low a limit that grave hepatic damage is no longer in doubt, and the time for successful treatment is past. Moreover, not only must the power of the liver to undergo compensatory hyperplasia be remembered, but its various functions not being equally inhibited by disease, it is necessary to apply tests covering different fields of hepatic activity.

In the first place I shall consider the action of the liver in preparing the three foodstuffs for the tissues, and the tests related to each.

The Work of the Liver in General Metabolism.

1. *Protein.*—It has been clearly recognized for some years that the protein molecule is broken down into its ultimate amino-acids before absorption, and that these end-products are less toxic than the intermediate proteoses and polypeptides from which they arise. Further, as there is a chemical specificity of tissues, by no means all of such end-products are capable of being utilized for tissue repair at the time of their

entering the blood-stream. Those which cannot be used at once by the tissues are turned into urea and other excretory products. Indeed, the method of maintaining the nutrition of the body is as far as possible the same on an ample protein diet as in starvation. In both, amino-acids are used to make deficiencies good, though in starvation they are obtained by pooling the autolytic products obtained, as it were, by levying a tax on all the cells of the body. From this pool individual organs are allowed to draw, according to their functional importance to the body. But even in the well-fed body the excess of protein food above what is required for tissue repair is not stored but excreted. Naturally, therefore, much more nitrogen is excreted by the well-fed than by the starving body, any storage being provided from non-nitrogenous sources.

It would appear that each amino-acid has its own method of breakdown, and very probably its own ferment for achieving that purpose. This has been brought out clearly by Garrod in his study of the inborn errors of metabolism. He says:

'If any one step in the process fail, the intermediate product in being at the point of arrest will escape further change, just as when the film of the biograph is brought to a standstill the moving figures are left, foot in air.'

Now it happens that most of such inborn errors as alkaptonuria, pentosuria, and cystinuria are inconvenient rather than serious. They are also rare, and

although their study has established points of great theoretical importance as to protein breakdown, they do not throw light on the estimation of hepatic efficiency. The ferments involved are evidently very resistant normally, since these substances do not appear in extensive degenerations of the liver, although porphyrinuria, which is sometimes an inborn error, may also occur in hepatic disease. The detection of leucin and tyrosin in the urine was thought at one time to be evidence of failure of the liver to turn them into urea, but they are now regarded merely as signs of hepatic disintegration. Though most prominent in acute yellow atrophy, they may be found in other diseases. Thus I saw them in a case of cirrhosis, where a severe hæmatemesis had been followed by coma for forty-eight hours, yet ultimately recovery took place. But it must be admitted that nothing has been found clinically to correspond to the experimental results obtained by Eck's fistula, even, for instance, after the Talma-Morrison operation.

It will be remembered that Eck made a fistula between the portal and hepatic veins in dogs, so that food entering the blood-stream after absorption from the bowel could pass into the general circulation without passing through the liver. He found that toxic symptoms resulted, especially after protein foods. The dogs, indeed, learned this for themselves and avoided animal flesh if they could obtain other foods. The liver also appears to destroy purin bodies, ultimately oxidizing them to urea.

The nitrogen partition test aims at determining any loss of the dis-aminating and urea-forming functions of the liver by comparing the ratio between the output of urea and other nitrogenous substances. *A priori* one would expect to find that in failure of hepatic efficiency the urea excretion would fall, while the excretion of the precursors of urea such as ammonia and amino-acids would rise. But in practice we are met with the following difficulties: (1) Quite a small proportion of the total liver substance is adequate to make the normal amount of urea. (2) As so much of the urea comes direct from the food, the total amount excreted varies with the diet. On a liberal protein diet the urea forms about 86 per cent. of the total nitrogen, while in the healthy fasting individual it forms a much smaller proportion. This variation seriously affects nitrogen partition, without implying any disease. (3) An absolute increase in ammonia formation may be, and usually is, simply a protective step against acidosis, and is not evidence of a failure of urea formation. (4) Variations in the kidney

otherwise, implies a failure of renal function in pregnancy. This adds to the difficulty in applying nitrogen partition tests to the hepatic toxæmias of this condition.

2. *Carbohydrates.*—All sugars are absorbed as monosaccharides. Although they can be rapidly stored in the liver and muscles as glycogen, the absorption from the alimentary tract of any such sugar, with the important exception of lævulose, leads to a rise of blood-sugar from the fasting level of 0·1 per cent. to something like 0·16 per cent., falling again in about one and a half hours. This would imply that lævulose, although its limit of tolerance tends to be rather lower than that of dextrose, can within that limit be stored as rapidly as it can enter the blood-stream. Years ago H. Strauss regarded a diminished tolerance for lævulose as evidence of impaired hepatic function, but this did not afford a satisfactory basis for a test. It is not sensitive enough, and the kidney threshold for the excretion of sugars is not a constant. Maclean and de Wesselow, having determined that lævulose when given by the mouth in doses of from 30 to 50 grammes does not raise the blood-sugar in healthy subjects with an intact liver, went on to show that when the liver is defective it is not able to store lævulose fast enough to prevent it from entering the blood-stream, and thus increasing the blood-sugar proportionately to the hepatic defect. This is the basis of the modern lævulose test, which seems to me one of the best we have for hepatic efficiency. According to Spence, it shows that so-called catarrhal jaundice cannot be due to mere ascending

catarrh of the main bile-ducts, but must involve some hepatitis, since administration of lævulose raises blood-sugar in this disease even before the onset of jaundice. It has enabled several observers to show a similar change in salvarsan poisoning, while Mackenzie Wallis has found that in every case where a course of such an arsenical preparation has been given, some degree of hepatic inefficiency exists for at least three months. Clearly a second course should not be given within this interval; while, if lævulose causes a rise of blood-sugar of 0·05 per cent. above the fasting level, careful treatment is required, however slight the other clinical manifestations may be. In pure obstructive jaundice this rise of blood-sugar does not occur, or is very slight. As further evidence that catarrhal jaundice may involve a toxic hepatitis I should like to refer to a group of cases I saw in 1922, where, in addition to a large and tender liver, with jaundice, there was cyanosis, air hunger, and almost complete suppression of urine, followed by intense albuminuria, sometimes with hæmaturia and casts. Yet the patients made a good recovery, and soon became free from albumin. Sometimes they showed an increased diastase output, which might be held to prove pancreatic involvement as well.

The diastatic function of the liver has already been referred to in connection with the pancreas. So far, however, though gross increase in diastase output certainly suggests pancreatic insufficiency, a defect of diastase in the blood has not helped much as evidence of hepatic insufficiency. Harrison and Lawrence

found in twenty cases of hepatic disease that the blood diastase was low in three severe cases. In two this rose again as the clinical condition improved. Certainly defective output in the urine could not provide such evidence because of the behaviour of the threshold of the kidney.

One thing appears clear about the glycogenic function of the liver: in the presence of an ample supply of glycogen the metabolism of the liver proceeds more smoothly. It was first stated that it was the antitoxic power of the liver which chiefly was affected by the glycogen store. But it seems more far-reaching than this, though it is certainly true that a liver is less liable to post-anæsthetic poisoning if it is well supplied with carbohydrate, while starvation, which would deplete the glycogen store, increases the liability to this catastrophe. And Colonel Harrison, at Maclean's suggestion, has found giving sugar, usually dextrose, of material benefit in preventing toxic jaundice after salvarsan. In a group of patients receiving sugar before injection there were only two or three cases, while in another group not receiving sugar there were nearly fifty cases of toxic jaundice. Glycogen, whether formed from dextrose or levulose, appears to be the same—and it can be readily drawn upon by the blood and tissues, being converted into dextrose in order to supply sugar to the latter. This glycogenic function appears to be controlled by a reversible ferment, which can make and unmake glycogen in accordance with the body's needs.

3. *Fats.*—Fat in the liver may be obvious as the result of sepsis, broncho-pneumonia, phthisis, rickets, profound anæmias, and poisons, such as phosphorus, chloroform, and trinitrotoluene. But the amount of obvious fat is not an accurate criterion of the total fat in an organ. Combined fat in the heart, kidneys, or liver will not react to stains such as osmic acid or Sudan red, or even yield to fatty solvents, while when it is set free by degenerative processes, it will do so readily. Again Rosenfeld showed that 'fatty infiltration' of the liver may really be due to transference from other parts. The condition may fairly be called one of 'fatty congestion.'

Leathes has shown that the fat normally present in the liver is in the more active unsaturated form, but that the fatty deposit which occurs there in poisoning by phosphorus or tetrachlorethane or after anæsthetics is in the more inert, saturated form. He makes out a good case for regarding as a function of the liver the conversion of saturated fat into the more active unsaturated form for utilization by the tissues. When the liver is thrown out of gear by various toxins the tissues, starving for prepared fats, send unprepared fats to the liver, but in vain, for it is unable to deal with them. The liver may be compared to a miller—the saturated fats are the wheat he grinds, and the unsaturated fats are the flour that results.

Foulerton pointed out that chloroform, ether, and tetrachlorethane are solvents of fat, while phosphorus, dinitrobenzol, and trinitrotoluene are readily soluble in fats, so that the destructive effects of these poisons

on the liver may be due to their being conveyed with the fats to the liver in the attempt to carry out this process. In some cases, such as phosphorus or post-anæsthetic poisoning, this carriage of fats may lead to a gross increase in the size of the liver, but we require a much more sensitive test than this. Whipple devised the lipase test to this end. Normally blood contains a small constant amount of fat-splitting ferment, but in diseases of the liver this lipase is increased, as measured by the power of the blood to split ethyl butyrate. It has been supposed, therefore, that normally the liver inhibits the formation of lipase, so that its increase in the blood is a measure of hepatic damage. Whipple has applied this to chloroform poisoning, and Mackenzie Wallis to salvarsan poisoning. The damage has, however, to be rather gross before the lipase increase is enough to be relied upon.

The latter observer has further reported that in toxic jaundice due to salvarsan poisoning the cholesterol in the blood is diminished, while in this condition and in phosphorus poisoning the liver is found loaded with cholesterol esters post mortem. This suggests that the liver normally plays the same part both in cholesterol and fat metabolism. It may be, however, that the cholesterol is merely on its way to be excreted in the bile, but the diseased liver cannot accomplish this. Its presence in the kidney under similar conditions may be an attempt at an alternative channel of excretion. In the toxæmia of pregnancy, including a case of icterus gravis, this cholesterol disturbance was not found.

The Antitoxic Functions of the Liver.

At the risk of anticipating what is dealt with under intestinal intoxications, we may say that apart from the reactions against bacterial poisons the antitoxic processes of the body are few and simple—such as oxidation, reduction, hydration, dehydration, and methylation. The protective substances are few, and the process of rendering a poison harmless by conjugating it with a protective substance is most often carried out by the liver. Thus the toxic indol is conjugated with sulphuric acid into a harmless ethereal sulphate, indican. Although we regard marked indicanuria as evidence of intestinal toxæmia, we must remember that we are testing for that part of the indol which has been rendered innocuous. A more accurate method is to estimate the ratio between ethereal and total sulphates; the larger fraction the former constitutes of the latter the nearer are we to the limit of the antitoxic power of the liver. But if the liver cells are diseased such conjugation cannot occur, so that toxic substances like indol, skatol, and phenol can pass direct into the blood, even though the urinary output of ethereal sulphate is low. There does not appear to be any simple test for recognizing this.

Glycuronic acid is another important protective substance, and the formation of harmless glycuronates after administration of camphor, morphine, and the like is a function of the liver. It is claimed that 7½ grains of camphor given by the mouth should be

completely conjugated with glycuronic acid and recognized by its reducing action in the urine, but if the liver is diseased no such glycuronic acid is formed. A simpler test is that introduced by Roch. He gives half a grain of sodium salicylate an hour before food. This should be turned into a glycuronate, which would not yield a purple colour with 1 per cent. ferric chloride solution. If the urine excreted for the four hours after a meal does give this colour, hepatic insufficiency is present.

The *hæmoclasic crisis* may also be regarded as due to a failure of the antitoxic power of the liver. As C. M. Wilson expresses it, under this rather forbidding name is concealed a test disarming in its simplicity. Widal maintained that when the liver was diseased the normal post-prandial leucocytosis was replaced by a leucopenia, which was accompanied by a fall of blood-pressure. This was believed to be due to the hepatic failure permitting the entrance of incompletely digested proteins into the systemic circulation. It recalls the anaphylactic reaction to material unsuitable for assimilation. Before breakfast a white count is taken, then 7 oz. of milk are drunk, and another count taken twenty minutes later. Wilson concludes that, with the possible exception of the levulose tolerance test, this is the only test which gives an early warning of hepatic insufficiency.

The functions of the liver with regard to maintaining the coagulability of the blood are not yet sufficiently understood to discuss their clinical application.

The Secretion and Functions of Bile.

Bile is partly an excretion which is going on continually, partly a digestive fluid, which is only required during digestion. The gall-bladder allows a discontinuity of entry into the bowel of a fluid which is being continuously formed. Furthermore, the gall-bladder, by adding cholesterol and mucin to the bile while absorbing water, alters its composition, making it more concentrated and viscid. Therefore, the longer bile remains in the gall-bladder the thicker it becomes, while with complete obstruction to the cystic duct the bile entering the intestine is unusually dilute. The bile pigments bilirubin and biliverdin are purely excretory, and their origin will be considered later. Bile also contains lecithin (a complex phosphorized fat) and, as stated above, cholesterol, which is a monatomic alcohol, with mucin, as well as inorganic salts, which render it alkaline. But the important secretory constituents of bile are the bile salts. These are sodium taurocholate and sodium glycocholate. The cholalic acid is secreted by the liver cells, and it is not found when the liver is excluded from the circulation. It is conjugated with taurin and glycin. Glycin is amino-acetic acid, while taurin is a sulphur containing body derived from cystin. If cholalic acid is given it produces a considerable increase of bile acids in the bile, but as this does not follow the administration of taurin it would appear that under normal conditions of health and diet there is always an excess of taurin

present, and that the output of bile acids depends on the amount of cholalic acid available. Normally the outflow of bile is strictly parallel with the pancreatic secretion, though smaller in volume, the total amount secreted in the day averaging 30 ounces. The outflow of bile into the intestine depends upon—

1. *The Rate of Secretion.*—Secretin will double the secretion of bile, thus illustrating the co-operation of the liver with the pancreas. The absorption of bile salts also increases secretion, while salicylate of soda promotes a flow of dilute bile.

2. *Diet.*—Protein has the most effect, fat next, while carbohydrate has the least influence.

3. *The Activity of the Muscular Walls of the Adjacent Passages.*—The gall-bladder shows rhythmical contractions, resembling peristalsis in being independent of the central nervous system. When peristalsis is increased in the bowel these contractions of the gall-bladder are increased. Thus it comes about that most so-called cholagogues, such as calomel, are merely indirect in their action. They do not increase the secretion of bile, they merely help to empty the gall-bladder by increasing peristalsis.

4. *The Influence of Extrinsic Nerves.*—As with the bowel and other hollow viscera the sympathetic relaxes the body of the gall-bladder while closing the sphincters at the neck of the gall-bladder and at the point of entrance into the bowel. Hence the effect of reflex irritation—*e.g.*, in the appendix, in holding up the output of bile. The stimulation of the vagus, on the

other hand, probably leads to contraction of the gall-bladder.

5. *The Pressure of Adjacent Organs.*—The movements of the diaphragm help to express the contents of the gall-bladder. Hence the influence of tight lacing in producing stagnation of bile. But even without this, the fact that women use their diaphragm less than men renders them more liable to this condition.

The Actions of Bile—may be classified thus.

1. *On Digestion.*—Beyond the precipitation of acid albumin by neutralizing the gastric juice, bile does not appear to have much action on proteins, though Pavloff believes it assists trypsin. It certainly accelerates the action of amylopsin in digesting starches. The activity of pancreatic juice in splitting fats is trebled by the addition of fat whether boiled or unboiled. This is due to (*a*) *the bile salts* which lower surface tension and thus permit of closer contact between watery and oily fluids, (*b*) *cholesterol and lecithin* which help to dissolve fatty acids and soaps, including even the otherwise insoluble calcium and magnesium soaps. Even in acid media this action continues because bile acids dissolve fatty acids.

2. *On Absorption.*—Here again it is the lowering of surface tension by the bile salts which promotes the absorption of fats.

3. *On Peristalsis.*—Bile salts appear to increase the movements of the intestinal muscles and of the muscles of the villi. They are therefore natural laxatives.

4. *On Putrefactive Processes.*—Though bile acids are

antiseptic, bile salts are not. They merely diminish putrefaction by promoting absorption.

It should be noted that only traces of bile salts are present in fæces. They are absorbed by the villi, presumably with the fats, and conveyed to the liver where they are used over again. This is known as Schiff's biliary cycle. Copeman showed that when a biliary fistula permits the escape of bile on to the surface of the body, so that this cycle cannot occur, the amount of bile salts in the bile soon falls to one-tenth of its former figure.

If bile fails to enter the bowel, the ill effects are principally due to the absence of bile salts. As they help in the emulsification and absorption of fats which have been previously split into fatty acid and glycerin by the pancreatic juice, the steatorrhœa which follows biliary obstruction is due to the increase of soaps and fatty acids in the stools, while in failure of the pancreatic secretion it will be the unsplit or neutral fat that will be in excess. Interference with absorption of proteins will lead to increased intestinal putrefaction with a consequent increase in the indican of the urine. The absence of bile pigment from the stools causes the familiar clay colour, but as the excess of fat may mask the presence of a small amount of bile we must not conclude from this colour alone that no bile is entering the intestine. Extraction of such fæces with acid alcohol or amyl alcohol may still show the presence of urobilin by the band in the blue of the spectrum or by green fluorescence on the addition of zinc chloride and

ammonia. This would indicate incomplete obstruction, such as is usual with gall-stones, while the entire absence of urobilin is suggestive of the more complete obstruction produced by new growth of the head of the pancreas. The presence of obvious bile pigment in the stools in a case of jaundice is, of course, against its being of obstructive origin.

Apart from hepatic colic the presence of gall-stones may disturb digestion in several ways, as may cholecystitis. Flatulent dyspepsia is the rule. H. E. Griffiths confirmed the general clinical impression that gall-stones produce reflex hyperchlorhydria by finding this in 90 per cent. of the test meals on his cases. If this was not accompanied by regurgitation into the stomach there was usually X-ray evidence of marked pylorospasm. He attributes this regurgitation to the unregulated flow of bile into the duodenum which follows such diseases of the gall-bladder as render it incapable of acting as a reservoir. A rise in the alkalinity of the duodenum at inappropriate times would relax the pyloric sphincter. This would occur when the cystic duct is occluded, or where the muscle of the gall-bladder has been replaced by fibrous tissue as the result of prolonged disease, but would not follow complete obstruction of the bile-duct, which would diminish the alkalinity of the duodenal contents. If it agrees with the other findings we may consider hyperchlorhydria to be the rule with disease of the gall-bladder and bile-ducts, while if there is regurgitation as well there is probably chronic disease of the gall-

bladder itself. Additional interest has been aroused in this part of the subject by the claim that if 1 to 4 drachms of magnesium sulphate in concentrated solution be introduced into the duodenum by the Einhorn tube a sharp flow of bile is excreted by reflex contraction of the gall-bladder. This can be removed from the duodenum for examination. This claim has been disputed, and it is clear that if there is complete obstruction of the bile-ducts the method is not applicable. But that it is occasionally of service is shown by a case in which I diagnosed inflammation of the gall bladder as the cause of dyspepsia. By this method purulent fluid was obtained, and at operation empyema of the gall-bladder was found. Lyon has extended the method by collecting three samples of bile by the duodenal tube. The first sample should be of transparent, yellow-golden colour from the common duct, the second darker and more viscid from the gall-bladder, and the third much thinner and lighter in colour from the hepatic and intrahepatic ducts. By examination of these he claims that infection and inflammation of the various parts of the biliary system may be located.

I recently had an interesting case in which Mr. Griffiths obtained pus in the second sample by this method, and I afterwards treated on the plan I generally employ for cholecystitis. For five days a mixture is given three times a day containing 10 minims of tincture of belladonna to dilate the bile passages and 10 grains of salicylate of soda to dilute the bile, together with some bicarbonate of soda and infusion of gentian.

Antiphlogistine is applied hot over the gall-bladder during this time, while the patient is directed to drink water freely so as to help the flow of bile. Then some compound of hexamine, such as helmitol 10 grains twice or thrice a day, or a tablet of Felamine (which is a compound of cholalic acid and hexamine) is given with a glass of water. While it is doubtful whether hexamine itself can liberate active formaldehyde in the alkaline medium of the gall-bladder, the claim that these substances can appears to be justified. For I saw a case of a typhoid carrier (who had a gall-stone, as such patients usually have), treated by helmitol after operation; for two hours after each dose the bile escaping by the fistula was colourless. Now reduced bile is almost colourless, and formaldehyde is a reducing agent. The patient who yielded pus from the gall-bladder by Einhorn's tube improved greatly under the belladonna and salicylate treatment and became free from symptoms, but still desired operation, as she was a stewardness on a liner and feared the risks of an acute attack while at sea. Mr. Harold Wilson accordingly operated, but found the gall-bladder normal. The evidence of the effectiveness of the treatment, at any rate in this case, appears to be complete.

The dietetic principles underlying treatment are that meat extracts, purins, and condiments, help to produce hyperchlorhydria; soft carbohydrates and green vegetables promote flatulence. The fats, while diminishing the secretion of acid in the gastric juice, depend on bile for their absorption, and if not absorbed they

increase intestinal putrefaction by coating over the proteins; moreover, their influence in producing obesity must not be forgotten. The practical deductions from these considerations are: (1) White fish, eggs, cheese, mutton and chicken may be allowed, while soups, broths, liver, kidney, sweetbreads, and rump-steak should be forbidden until the hyperchlorhydria is checked. (2) Dry forms of carbohydrate, such as biscuits, rusk and toast are preferable to bread, ground-rice puddings and the like, because they demand thorough mastication before they can be swallowed, and therefore undergo a considerable degree of digestion by the saliva. (3) Sweets can be selected from jelly, egg custard, omelette, junket and stewed fruit. (4) At first vegetables had better be barred altogether, for, though cellulose is an aid to peristalsis, it promotes flatulence. As the patient's intestinal condition improves, this rule may be gradually relaxed. (5) Fats, in the form of butter, cream, or fat meat, should only be allowed in small amounts for the reason given above.

It is important that water should be drunk freely to prevent inspissation of the bile. Patients do not care to be told to drink water from the tap, preferring, as of old, the waters of Abana and Pharpar. It is well, therefore, to select a spring which is mildly aperient, slightly alkaline, and not too highly mineralized, such as Rosbach, Apollinaris, St. Galmier, Vittel (source salée) or Evian. The sulphur waters of Harrogate are recommended by some. Salutaris water has the advantage of not being mineralized at all.

Jaundice.

Jaundice is the classical example of a striking symptom of varying significance. Recent work has thrown new light on this. As with diabetes and nephritis, the centre of interest has shifted from the urine to the blood.

Slightly modifying McNee's conception of the structure of the liver, we may compare each lobule to a series of radiating tubular glands, shaped like test-tubes with the closed ends pointing to the centre of the lobule. The test-tube is lined with polygonal cells and its lumen represents the bile capillary. These test-tubes are packed in saw-dust, which represents large endothelial Kupffer cells lining the wide capillaries of the portal vein. The polygonal glandular cells are not concerned with the manufacture of bile pigments, but merely transfer it from these vascular capillaries to the bile capillaries, modifying it in the process.

The Kupffer cells are a part of a much more widely distributed 'reticulo-endothelial' system, which is also found in the spleen, bone marrow, lymphatic glands, interstitial cells of the testes, reticular cells of the thymus and capillary endothelium of the adrenals. This system appears to be concerned in the metabolism of hæmoglobin and of fats, especially the lipoids. In excessive blood destruction its cells take up both intact and broken-down red corpuscles, as well as free hæmoglobin by phagocytosis. The iron containing part of the hæmoglobin molecule is broken off as hæmo-

siderin, which can be demonstrated by the Prussian blue reaction, while the hæmatoporphyrin becomes altered to form bile pigment. In health this work is largely done by the spleen, but when blood destruction is excessive other parts of this system may help. Now Van den Bergh has applied Ehrlich's diazo reaction to the detection of bile pigments in the blood serum, and has found that bilirubin may be present there in two different forms; while biliverdin does not give this reaction at all. Some sera would give a colour reaction at once—*the immediate direct reaction;* others would give only a *delayed reaction,* or no reaction until after precipitation with alcohol—the *indirect reaction.* Others again, as shown by Feigl and Querner, give a slight reaction at once, deepening later, or on the addition of alcohol—the *biphasic reaction.* It is found that bile from the gall-bladder, which has, of course, passed through the liver, always gives an immediate direct reaction, while bilirubin obtained from old hæmorrhagic effusions (which has been formed apart from the liver cells) gives a delayed or indirect reaction. The suggestion is that the work of the liver is to give the final touch to the manufacture of bilirubin, probably breaking it off from some other constituent of the serum, and that it is only in this final form it can give the direct reaction. In its combined form it can only give a delayed or indirect reaction. When both forms are present the reaction is biphasic. Jaundice might therefore arise in several different ways, and we may adopt McNee's classification.

1. *Obstructive Hepatic Jaundice.*—Here the bile has been duly passed into the bile capillaries, but is obstructed in its outflow, and is therefore reabsorbed into the blood-stream. Van den Bergh's test will give the immediate *direct reaction.* Moreover, such bilirubin being in its final state can be oxidized into biliverdin more easily than the other variety. This is the condition found in the jaundice of gall-stones and new growth of the head of the pancreas, for instance. Van den Bergh adopted as his unit the presence of one part of bilirubin in 200,000 parts of serum. In this type of jaundice 50 units may be found. In gall-stones without jaundice the bile content of the serum is normal.

2. *Toxic and Infective Jaundice.*—Here the polygonal cells being diseased, some of the bilirubin from the Kupffer cells is unable to enter them, and therefore passes direct into the blood-stream. The blood serum will, therefore, yield at first an *indirect reaction,* but as disintegration of the cells proceeds the bile capillaries become obstructed also and the reaction becomes *biphasic,* the direct portion of the reaction becoming intenser as obstruction becomes more marked. Such jaundice occurs—

(*a*) As a complication, of acute fevers, such as pneumonia, typhoid, and spirochætal jaundice.

(*b*) After certain drugs, such as chloroform, phosphorus, and salvarsan.

(*c*) After damage of an unknown kind—acute and subacute yellow atrophy.

(*d*) After many general conditions of infection and toxæmia. Here the jaundice does not appear to be merely due to catarrh of the smaller bile-ducts as was formerly thought, for a series of changes in the liver cells can be demonstrated, ranging from simple cloudy swelling (as in pneumonia), through fatty degeneration (as in chloroform poisoning), partial necrosis, and dislocation of the liver cells (as in spirochætal jaundice), to almost complete necrosis (acute yellow atrophy). In salvarsan poisoning any one of these stages may be met with.

3. *Hæmolytic Jaundice.*—When blood destruction is excessive more bile pigment is formed than the polygonal cells can deal with; some will be excreted normally, while the rest goes into the blood in the combined form. The serum will, therefore, only yield the *indirect reaction,* and bile pigment will usually be absent from the urine, while constantly present in the fæces.

That blood pigment can be turned into bile pigment without the aid of the liver was shown by Virchow. The hæmatoidin of old blood clots is clinically identical with bilirubin in its combined form, yielding the indirect reaction, as we now know. The experiments on geese which were formerly held to prove the contrary were done in ignorance of the fact, that what corresponds to the spleen in higher animals is largely enclosed within the liver of birds. McNee suggests that hæmolytic jaundice depends on blood destruction in excess of normal, whereby the cells of the reticulo-endothelial

system, especially in the spleen, are thrown into increased activity, which may result in or be actually dependent on an increase in the size of the spleen. The blood serum comes to contain a greatly increased amount of bilirubin of the same type as that arising from the physiological destruction of effete red corpuscles in health.

This conception would explain much which has been hitherto obscure. It has been recognized that 'splenic anæmia' is a consequence of several different conditions producing splenic enlargement, and that it is often relieved by splenectomy. On removal the spleen may be found to be the seat of tuberculosis or endothelioma, among other conditions. Apparently we may now conclude that any disease of the spleen *stimulating the formation* or activity of the reticulo-endothelial cells sufficiently may produce splenic anæmia. It would also explain why splenic anæmia may go on to Banti's disease, in which cirrhosis of the liver and jaundice supervene, since the Kupffer cells of the liver are structurally and functionally an extension of the reticulo-endothelial system of the spleen. It explains why the spleen may enlarge in the crises of pernicious anæmia and throws light on the occasional jaundice (without necessarily biliuria) in that disease.

Van den Bergh has also shown that in some apparently healthy sallow individuals the bilirubin in the serum may reach nearly three units. Since the threshold for its excretion in the urine is 4 units such individuals show no bile in the urine. The condition has been

called 'simple familial cholæmia'; usually the spleen is not enlarged nor the fragility of the red corpuscles increased. There would appear, however, to be all stages between this and the condition known as acholuric family jaundice. Here the patient may be born jaundiced or become so soon after birth. The jaundice persists with little or no variation for many years, but bile pigment is present in the stools as in health, while it is absent from the urine, in which any darkening present is due to excess of urobilin. Nevertheless, bile pigment, giving the indirect reaction, is present in the serum. The spleen is always enlarged. There is considerable anæmia with a low colour index, poikilocytosis, nucleated red cells and reduction in the number of leucocytes. Yet the patient has good or fair health, and shows a normal resistance to intercurrent diseases. This condition tends to appear in more than one member of the family and in successive generations. Some of the patients are liable to attack during which the colour deepens, when pain may be experienced over the spleen or liver, or both, and there may be slight pyrexia. Alcohol and syphilis do not appear to play any part in the ætiology. Enlarged abdominal veins, ascites, œdema of the legs and hæmatemesis have never been recorded, and the liver does not appear to be cirrhotic, although it is sometimes fatty.

Attacks of hæmoglobinuria have been noted in this condition, which could be produced by exposure to cold, and in this connection it is interesting to note that in one family a cold bath would intensify the

jaundice. All this points to hæmolysis as a cause of the jaundice. The serum from a patient agglutinates normal red corpuscles, but not his own red corpuscles or those from another individual suffering from the same disease. The most striking pathological feature of the condition is the undue fragility of the red corpuscles, for they are hæmolyzed by a dilute salt solution which has no effect on ordinary corpuscles. We may conclude that in acholuric family jaundice there is a chronic hæmolysis of unduly fragile corpuscles as a primary event, but that the threshold for the excretion of bile is not reached, while the enlargement of the spleen and liver is secondary, to deal with the increased hæmolysis. What the cause of this undue fragility may be is still unknown.

Latent Jaundice is a term applied to conditions where the bilirubin content of the serum does not reach 4 units, so that the usual symptoms are missing. The hæmolytic type of this is seen in pernicious anæmia, anæmias due to worms, and in all the newly born. Its occurrence is of prognostic value when salvarsan is being given, as it is evidence of the approach of poisoning by the drug. An obstructive type of latent jaundice occurs in cirrhosis. In this connection it is interesting to note that in the ordinary jaundice so common in the new-born (icterus neonatorum), the blood serum gives an indirect Van den Bergh's reaction, so that it is hæmolytic in origin. Before birth the fœtus has a polycythæmia reaching about 6½ millions per c.mm. On the second day after birth this excess

has disappeared, and probably there will not be more then $4\frac{1}{2}$ millions. In a sense this polycythæmia may be regarded as a protection against the risk of loss of blood at birth. Once this has passed, hæmolysis occurs, and obvious hæmolytic jaundice may follow. The fact that latent jaundice is constant after birth supports this view. Severe jaundice in the new-born is generally due to suppurative pylephlebitis from septic infection through the umbilical cord or to congenital syphilis. Rarely it results from congenital atresia of the bile-ducts.

Dissociated Jaundice has been described by French observers—the bile pigments going one way, the bile salts another. But as they did not take the condition of the blood into account, judgment must be reserved on this. There may, indeed, be renal dissociation in obstructive jaundice, both pigments and salts being found in the blood, while only bile salts are filtered out by the kidney. I saw a case of catarrhal jaundice, in which bile salts appeared in the urine before the pigment, and it is stated that this is common in the later stages of the condition. In my experience of jaundice as a whole the converse condition is commoner—*i.e.*, for bile pigment to be present in and bile salts to be absent from the urine.

The effects of the failure of bile to enter the bowel have already been considered. We may now turn to the other effects on the body of the alteration in the course of the bile.

The Urine.—The best test for bile pigments is

Gmelin's: the play of colours obtained by successive stages of oxidation with fuming nitric acid, green being the most important tint to look for. Rosenbach's modification of dipping filter paper into the urine and then placing a drop of nitric acid on the paper is the easiest way of performing the test. The green colour given on pouring tincture of iodine on to the surface of the urine is not so sensitive a test, and usually succeeds when the jaundice is obvious. Huppert's test enables us to extract bile pigment from a urine containing other pigments. Ammonia and calcium chloride are added to urine, and the precipitate which forms is collected on a filter paper and washed. The precipitate is then boiled with alcohol acidified with sulphuric acid, when an emerald green solution results.

The only test of any value for bile salts in urine is Matthew Hay's test. Flowers of sulphur poured on to the urine sink if bile salts are present, owing to reduction of surface tension. No other test is sensitive enough to recognize the small quantity found in urine.

The Blood.—It has now been conclusively demonstrated that in jaundice the bile enters the blood-stream rather than the lymphatics, appearing there within two hours after the experimental ligature of the bile-duct. Bile salts *in vitro* have a marked hæmolytic action due to their solvent action on the lecithin and cholesterin of the red corpuscles. And the serum of a jaundiced patient will hæmolyze foreign corpuscles readily, so that it may be impossible to carry out Wassermann's test, because hæmolysis occurs in all the

tubes. But in the body the patient's own red corpuscles acquire a heightened resistance against bile salts, which increases with the intensity of the jaundice. This sharply differentiates ordinary jaundice from acholuric family jaundice, in which the red corpuscles are unduly fragile. Occasionally small subcutaneous hæmorrhages may occur, but more usually the hæmorrhagic marks on the skin are produced by scratching excited by the pruritus, or are really small telangiectases.

The Heart and Vessels.—One of the most definite results of jaundice is bradycardia. High tension usually accompanies a slow pulse, but in the bradycardia of jaundice the pressure is low and the pulse dicrotic. High tension stimulates the cardio-inhibitory centre in the medulla, and thus slows the heart through the vagus, but bile salts have a slightly depressing effect on the heart. Hence the slow pulse with low blood-pressure. The action can be demonstrated easily on the isolated heart of a frog. As the effect can be abolished by atropine, bile salts probably act through the intracardiac endings of the vagus. The blood-pressure is also kept low by the toxic action of bile salts on the smaller bloodvessels producing some degree of vaso-motor paralysis.

The Central Nervous System.—Any severe toxæmic jaundice will be accompanied by marked nervous symptoms—headache, delirium, and ultimately coma. But this is due to the hepatic inadequacy caused by the action of the toxins on the liver and not to the jaundice. Indeed, bile salts are probably not produced

in this condition, the liver being too damaged to elaborate them. *A mild degree of poisoning of the nervous system by bile salt, is, however, common in ordinary* jaundice, causing headache and depression. Bile pigments and bile salts are generally found in the cerebro-spinal fluid removed by lumbar puncture.

The Skin.—Bile pigment usually appears in the skin soon after it does in the conjunctiva, but in the hæmolytic jaundice of pernicious anæmia the latter usually escapes. In obstructive jaundice the colour of the skin gives no indication whatever of the amount of bilirubin present in the serum. In the deep green jaundice of prolonged obstruction there may be less pigment in the serum than in early stages when the skin is just beginning to show a yellow tinge. This suggests that the skin is used as an alternative attempt at excretion, though, as will be pointed out later, it does not usually escape by the sweat. It is merely stored up in the skin, as if to free the more vital structures. Pruritus is a most troublesome symptom, but it is inconstant. It is due here, as pruritus always is, to currents of lymph set up between the prickle cells. Here the bile salts are responsible, as they cause alterations of surface tension which set up such currents. The patient indulges in much scratching, but without relief, for, as he often says truly, the itching is *beneath* the skin.

The Secretions.—Saliva, tears, and milk are not bile-stained in jaundice. It is frequently stated that the sweat is bile-stained, but this is exceptional. The

copious diaphoresis induced by pilocarpin is, however, accompanied by bile pigment. Nasal and bronchial mucus is not tinged with bile. Inflammatory and passive exudates are, however, invariably bile-stained. Thus if mastitis occurs in jaundice the milk will be coloured with bile. The expectoration in bronchitis is not coloured; but if pneumonia occurs as a complication bile at once appears in the sputa. Again, should œdema of the lung ensue the sputa becomes bile-stained. In a case of jaundice without pneumonia then occurrence of bile-stained sputa is of serious import, being evidence of heart-failure. Fluid in the pleural or abdominal cavity, being either the result of inflammation or of passive exudation, will, accordingly, be coloured by bile in a jaundiced patient.

The Fate of the Bile Pigment.—It will be gathered from what I have already said that I lean to the view that urobilin or its chromogen is formed in the intestine by reduction of bile pigment through bacterial agency. The evidence in favour of this seems very strong, for when all bile escapes through a biliary fistula, or when complete obstruction prevents bile from entering the intestine, no urobilin is found. Again, it is absent from the fæces at birth, not appearing till bacteria have had time to establish themselves in the bowel, while if bilirubin is inoculated with intestinal bacteria urobilin is formed. Normally this urobilin colours the fæces, where it is often called 'stercobilin,' while a small amount is reabsorbed and appears in the urine. If there is polychromia from increased hæmolysis there

will be increased formation of urobilin, while if there is partial or complete obstruction to the bowel there will be increased reabsorption of urobilin. In either case urobilinuria will occur, but it has most significance as evidence of hæmolysis. Against this view has been urged the presence of urobilin in the duodenal contents —that is, above the point at which bacterial activity begins. But I do not think this is sufficient to counterbalance the mass of evidence in favour of the intestinal origin of urobilin. I am aware that urobilinuria is often regarded as evidence of 'floating gall-stones' or of cholangitis. I can only say I have far more often seen this diagnosis made than confirmed, when based on this test.

In conclusion it will be observed that apart from an unpleasant but harmless discoloration produced by bile pigments all the important symptoms in jaundice are due to bile salts. Their absence from the intestine causes steatorrhœa and wasting from deficient absorption of fats, increased intestinal putrefaction and constipation. Their presence in the blood causes bradycardia, headache, depression, pruritus and sometimes subcutaneous hæmorrhages.

Treatment.—The treatment of jaundice must depend upon the cause, but the following general principles are usually applicable. During the initial stages the patient should be confined to bed. Although calomel is only indirectly a cholalogue it may be given in doses of ¼ grain every hour for six doses; this often relieves the vomiting, and has the additional advantage of being aperient without causing drastic purgation, which

should be avoided. Ten hours after beginning the calomel treatment a Seidlitz powder should be given, for repeated doses of calomel, if not effective in opening the bowels, may set up mercurial stomatitis. Alkalies are indicated as solvents of mucus in catarrhal cases, and, if the vomiting persists, may be combined with 10 grains of bismuth salicylate. As soon as the state of the stomach permits the more active sodium salicylate should be substituted as a diluent and disinfectant of the bile. In toxæmic cases the patient should be encouraged to drink large quantities of barley water and the like. With the onset of severe cases it is advisable to purge freely and to give an intravenous infusion of 1 drachm of sodium acetate in a pint of water at body temperature. Venesection has the advantage of removing toxins while the infusion is diluting them. Theocin-sodium-acetate in 2-grain doses is a useful diuretic. As dextrose is the most easily metabolized foodstuff in this state, it should be given by the mouth or rectum.

In even mild cases the diet will naturally be light. Milk is usually regarded as the mainstay, but owing to its comparative richness in fat it is not really suitable, and is often much disliked by the patient. I prefer to give barley water flavoured with lemon, with the white of an egg and a teaspoonful of Plasmon or Somatose to each half-pint. Tea is usually forbidden, though it is difficult to see on what grounds; jaundiced patients often crave for it, and if made in the Russian fashion without milk, but with a slice of lemon in it, seems free from objection. If the practitioner feels

reluctant to abandon milk, it should be separated or throughly skimmed to get rid of as much fat as possible, and then a grain of sodium citrate added to each ounce of milk to diminish curdling. Benger's food made with water, calves'-foot jelly and lemon sponge can usually be taken without difficulty. Alkaline mineral waters may be given freely.

When the bile pigment has returned to the fæces in obstructive cases, the patient feels much better, though still jaundiced; he can now get up and the diet should be cautiously increased. There is sometimes considerable depression during convalescence, for which strychnine and calumba may be given. Dilute nitro-hydrochloric acid in 10-minim doses is often recommended, but should not be given until all signs of obstruction have passed off.

For pruritus hot alkaline baths may be tried, or some of the following preparations: a lotion of 1 drachm of creolin and 1 ounce of glycerine made up with 10 ounces of water; an ointment of 20 grains of camphor, 30 grains of menthol and 1 ounce of vaseline; a dusting powder of 1½ drachms of camphor, ½ drachm of zinc oxide, and 1 ounce of starch powder; a paint or inunction of 2½ drachms of ichthyol, 3 drachms of absolute alcohol and ether to 2 ounces. Other preparations which may help are Eichoff's superfatted ichthyol salicylic acid soap, prepared by Muelhin's of Cologne, or 10 per cent. of anæsthesine in olive oil. As explained in Chapter I. thyroid extract in ½-grain doses may help by diminishing the formation of bile salts.

CHAPTER VI

URIC ACID AND THE PURIN BODIES

WE can only form an opinion as to the part that uric acid and allied substances play in disease by studying their normal behaviour in the body. Uric acid is a subject which has a peculiar fascination for the lay mind, and our patients often seek or wish to impart information concerning it. Again there is something about uric acid, as there is about alcohol, which seems to turn the mildest-mannered man into a heated partisan. The widest differences of opinion prevail; thus, while Haig regards it as the cause of nearly all the ills that human flesh is heir to, Luff looks upon it as a harmless by-product of metabolism. Between these two views there is plenty of room for the exercise of private judgment.

What are Purin Bodies? — Fischer gave the general name of purins to bodies containing the nucleus C_5N_4, which will yield two urea molecules on oxidation. Only twelve different purins are known to exist in nature, though 146 have been

prepared in the laboratory. The most important ones are—

Oxy-purins	Hypoxanthin ..	$C_5N_4H_4O$
	Xanthin	$C_5N_4H_4O_2$
	Uric acid	$C_5N_4H_4O_3$
Amino-purins	Adenin	$C_5N_4H_4NH$
	Guanin	$C_5N_4H_4O.NH$
Methyl-purins	Theobromine ..	$C_5N_4H_2(CH_3)_2O_2$
	Caffein and thein ..	$C_5N_4H(CH_3)_3O_2$

The source of urinary purins is partly from the food (exogenous), and partly from the tissues (endogenous).

1. *Exogenous Purins.*—We take these substances in, as—

(*a*) Methyl-purins in tea, coffee, and cocoa.

(*b*) Free purins, such as xanthin and hypoxanthin, in meat-extracts.

(*c*) Bound purins. Nuclei yield purins in their decomposition. The more cells a food contains the more nuclei it has, and therefore the more purins it yields. Accordingly, cellular organs, such as liver and sweetbread, are a great source of purin intake.

In the following table, taken from Walker Hall, the bound and free purins are estimated together, the foods having been weighed just as they are used in the household:

	Purins in Grains per Pound.
Fish:	
Cod	4·07
Salmon	8·15
Meat:	
Mutton	6·75
Beef	7·96 to 14·45

	Purins in Grains per Pound.
Meat:	
Chicken	9·06
Liver	19·26
Sweetbread	70·43
Eggs and cheese	almost 0
Vegetables:	
White bread, rice, cabbage, cauliflower, lettuce	0
Potatoes	0·14
Asparagus	1·5
Peas	2·54
Oatmeal	3·46
Beans	4·16
	Purins in Grains per Pint.
Beverages:	
Wines	0
Milk	0·0014
Beer	1·09 to 1·27
	Methyl-purins. Grains per Teacup.
Tea, China	0·75
Tea, Ceylon	1·21
Coffee	1·7

It will be seen from this table that the practice of distinguishing between red and white meats in dieting a gouty patient is apparently unsound if it is regarded as a method of regulating his purin intake. To cut a patient off mutton and give him chicken and sweetbread hardly achieves the object that is presumably in view.

Adler claims, however, that white meats lose their extractives more readily on cooking than do red; thus, veal loses four-fifths of its extractives, while beef loses

hardly any. Incidentally, the result of this must be that veal broth is laden with purins.

2. *Endogenous Purins.*—Even on a purin-free diet the urine contains purin bodies, so that some must come from the body tissues. Though the form of the purins may vary, the total remains fairly constant for the same person living under the same conditions, and amounts to about 0·2 gramme of purin nitrogen daily. An important source seems to be the leucocytes and the muscles. It has usually been assumed that it is the disintegration of the nuclei that provides the purin. But Plimmer believes that it is not when the leucocytes are being destroyed, but while they are active, that the output of uric acid is high. Thus, in pneumonia the increased output of uric acid runs parallel with the leucocytosis, and after the crisis, although there is a large destruction of leucocytes, this increased secretion of uric acid comes to an end. This is disputed by other observers. As for the muscles, during exercise there is merely an alteration in the proportions of the purin bodies. There is less uric acid and more xanthin and hypoxanthin. As the latter bodies are less oxidized than uric acid, it is probable that they replace it during exercise, because of the demands made elsewhere for oxygen. But after exercise, especially of an unaccustomed form, there is a considerable rise in the uric acid excretion. This might be explained by the washing out of retained uric acid by the more vigorous circulation induced, especially as repetition of the same exercise does not have the same effect. But Kenna-

way has found, so long as the form of exercise is varied, the increased output occurs. This, he considers, points to a heightened activity of the processes that form uric acid rather than to the sweeping out of it from the body. It is certain that the endogenous purins do not come from nucleo-proteins alone, for Garratt has shown that in fevers the rise in uric acid output is not accompanied by an increased output of phosphoric acid, which is a constant constituent of nucleo-proteins. Graham and Poulton conclude that purins are synthesized from proteins and carbohydrates, for a diminished intake of either leads to diminished formation of endogenous purins. The nucleins of the food do not appear to be utilized for this purpose. This accords with the clinical experience that excess of carbohydrate is bad for gouty subjects.

The Effect of Ingestion of Purin Bodies.—'If we believe popular medical, to say nothing of lay, opinion, uric acid is a virulent, all-pervading poison,' says W. G. Smith, 'yet it is a normal constituent of our bodies, and . . . is regularly found in the blood of birds.' Now, as Gore points out, 'uric acid can be no exception to the general law that a substance acts as a poison in direct proportion to the amount of it present in the circulating fluid.' We know that in leukæmia as much as 5 grammes of uric acid may be excreted in a day from the leucocytes. If uric acid is a direct poison, why does it not produce symptoms in leukæmia similar to those of 'uric acid diseases'?

Walker Hall thinks that, although purins have not

the powerful toxic properties usually ascribed to them, they are not entirely harmless. He tried the effect of taking considerable amounts while fasting, with the following results: 1 gramme of *caffein* caused a sensation of warmth in the abdomen and over the whole surface of the body. There was intense headache and some muscular twitching. On a second occasion a similar dose caused fulness in the head, a loss of muscular sense, and confusion of ideas. Half a gramme of *hypoxanthin* caused a slight fulness in the head, and a feeling of stiffness over the whole body. With *uric acid* a dose of ½ gramme caused distinct headache and confused ideas, with a sensation of warmth in the abdomen. On the second occasion the same dose caused slight headache, with sensory disturbances in the abdomen. On the third occasion a dose of 1 gramme caused no symptoms at all. Tolerance was therefore quickly established to doses of even 1 gramme, taken while fasting. This perhaps also explains the intolerance to purin-containing foods sometimes acquired by those who have adopted a purin-free diet.

Repeated injections of hypoxanthin into rabbits caused a cellular reaction in the liver and kidneys, and slow growth of the animal, but no rise of vascular tension was detected.

History of Purins after Ingestion.—After excision of a dog's kidneys, no uric acid or other purins can be found in the blood even on a diet rich in purins. This seems fatal to the hypothesis of 'retention' of uric acid, to which so many diseases have been referred.

Something must be able to destroy purins, probably intracellular ferments in the liver, since extracts of that organ cause uricolysis both *in vitro* and *in vivo;* while if the liver be excluded from the circulation, the uric acid in the blood and urine is increased.

Such food purins as appear in the urine have escaped by the kidneys before they could be destroyed in the liver. The amount has been stated to be from a quarter to a half of that ingested. In Plimmer's experiments, however, only one-tenth of the ingested purins, taken as herring roe, could be recovered from the urine. Kennaway found that while xanthin and hypoxanthin are proportionately more abundant with a copious flow of urine, the more oxidized uric acid is relatively more abundant in concentrated urine. In other words, the more rapidly excretion is going on, the more purins are removed before they can be oxidized. The final stage of the oxidation in the liver gives rise to urea. Hypoxanthin, xanthin, uric acid, urea, then represent successive steps in the oxidation of the purins, and the proportion in which they appear in the urine depends on the activity of the liver as compared with the rate of urinary excretion. An example of this is seen on comparing the urine in a case of failing heart with that of parenchymatous nephritis. In both the urine is concentrated, but in the former it is loaded with urates, while in the latter the urates are diminished, because, the excretory cells being damaged, and not merely congested, the liver can destroy purins more completely before the kidney can excrete them.

Plimmer found one condition in which ingestion of purins led to a considerable increase in their excretion. After giving Liebig's extract of meat, there was an increased excretion of uric acid equal to more than half the purins in it. This differed so widely from his other results that he made further investigations, and found that the meat-extract produced leucocytosis which may be accompanied by increased uric acid formation. He thinks that the leucocytosis was necessary to remove toxic substances contained in the meat-extract. If this be so, it raises doubts as to the wisdom of treating infective conditions by the artificial production of leucocytosis by nuclein injections, etc. Indeed, it has never been clear that such procedures do more than evoke enough leucocytosis to deal with the injected material.

Increased excretion of purins, then, may be due to—

1. An excessive intake of purins. But as long as the body is healthy, 90 per cent. of the purins ingested may be destroyed.

2. Defective action of the liver, which fails to break down the purins in the way it should.

3. Anything causing leucocytosis.

4. Unaccustomed muscular exercise.

The upholders of the uric acid theory of disease assume that the body can deal with its endogenous purins, but is poisoned by ingested purins. There is little in the history of purin metabolism to support this view. We have seen that there may be a great increase in uric acid production without gouty symp-

toms, and that a healthy liver has a great power of destroying purins. Moreover, a vigorous reaction of the body to infection is marked by an increased production of purins, and it is probable that the increased output of purins after giving meat-extract is simply due to the leucocytic reaction it induces. Leathes and others have shown that the quantity of uric acid excreted is greatest in the early waking hours of the day, and least during the night. In other words, its excretion runs parallel with bodily activity.

Purins and Gout.—I believe we may look upon a person who is readily poisoned by purins in the same light as those who have cystinuria, alkaptonuria, or pentosuria—*i.e.*, they all lack a link in the chain of protein katabolism, so that intermediate products appear in the urine instead of the usual end-products. The curious point, to my mind, about the man who cannot metabolize purins is his fixed belief that the rest of mankind suffers from a similar incapacity. Hence the elevation of the purin-free diet to the dignity of a cult.

If food purins lead either to a uratic deposit in the tissue or to a high purin output, it is a sign of hepatic insufficiency rather than the cause of disease. Amid all the confusion that reigns on the pathology of gout we can hold to the two definite facts established by Sir Alfred Garrod: in gout there is an excess of uric acid in the blood, and during the paroxysm a diminished output of uric acid in the urine. We may add that there is a retardation in the excretion of

exogenous purins. The whole reveals a deficiency in the capacity of the body to katabolize purins. Mere retention of purins will not *cause* gout. Uric acid can always be demonstrated in normal blood or lymph; in gout and lead-poisoning the amount is increased, though not so much as was formerly thought. The blood is capable of carrying much more sodium urate in solution than it is usually asked to do. Walker Hall had calculated that the average daily output could be suspended in the quantity of blood passing through the lungs in five minutes, or through the kidneys in twenty minutes. Even after severe muscular exercise or in fever the quantity eliminated is well within the suspension capabilities of the blood-stream. He considers that the small purin increased in the blood of a gouty individual cannot be responsible for the deposits in joints and tophi, since there is such a considerable margin of solubility available. Nor does the hypothesis of renal inadequacy provide a satisfactory explanation, since the kidney of diffuse nephritis, which is much more damaged than the gouty kidney, can excrete uric acid at a normal rate. An additional factor must come in, and, as Walker Hall says: 'Gouty individuals possess some inborn defect or alteration of nuclein metabolism which lowers the resistance of the tissues in certain directions, and so permits a response to irritants which are scarcely appreciated by those whose metabolism does not exhibit this peculiarity.' ~~Llewellyn~~ makes out a strong case for this irritant being an infection of low virulence.

It is only reasonable in such cases to diminish the intake of substances which are not necessary as foods, and which tax the liver to metabolize them, and the kidney to excrete them. But this will not satisfy the enthusiasts. Goodhart complains: 'It is diet, diet, diet, all the time for the man who passes uric acid. It is "get the uric acid out of your system," and all will be well. But though you absolutely exclude all uric-acid-forming food, of whatever kind you assume that food to be, you may wither up your patient into a shrivelled, juiceless, prematurely aged being, and there will yet, by some means or other, under favouring conditions, be squeezed out of his tissues enough uric acid to form a large deposit of red crystalline matter in his urine.' This accords with the experimental evidence that checking the ingestion of purins does not prevent their endogenous formation.

This modified conception of the source and history of purin bodies should diminish our ardour in trying to wash uric acid out of the system. 'Much therapy is directed against this necessary result of nuclein metabolism,' but, as a matter of fact, most drugs have an insignificant effect in increasing the elimination of uric acid and its allies.

Water, by producing diuresis, certainly increases the output. It is chemically impossible that *lithium salts* can have any such effect. We know that chemical action is determined both by the mass and the avidity of the various interacting bodies, but also that if in any mixture of acids and bases an insoluble salt can

be formed, it will be formed. In face of this, what can be the use of a few grains of lithia introduced into the body to combat an amount of sodium which, in addition to all the advantage of mass reaction, forms the less soluble salt? Lithium is, moreover, distinctly depressing in its action on the spinal cord, motor nerves, and alimentary canal.

Piperazin has been shown by Fawcett and Gordon to have no solvent action even in full doses. *Hexamine* can cause a very slight increase in the purin output.

The action of *alcohol* is complicated. With malt liquors there is an actual intake of purins, while in all cases alcohol leads to diminished solubility of purins.

Minkowski has suggested that *thyminic acid* (an organic acid containing phosphorus) is the substance which holds uric acid in solution in the circulation. Quadriurate of soda has for some time been regarded merely as a mixture. Thyminic acid can hold its own weight of uric acid in solution at 20° C., and 50 per cent. more at body temperature. Although we no longer believe that deposit of biurate of soda explains the whole pathology of gout, and look upon it rather as a symptom, yet we can quite understand that a case of gout would be improved if the deposit could be prevented. The drug is put up in tablet form under the name of Solurol, and is given in doses of 4 to 8 grains three times a day. But although it has been on the English market since 1905, the number of reported successes remains very small.

Salicylates can cause a very markedly increased out-

put—sometimes as much as 50 per cent. But it is not a little disturbing to find that this increase will occur even after a purin-free diet has been taken for years. There are three possible explanations:

1. That salicylate washes out retained uric acid. But since the liver rapidly destroys uric acid, retention does not occur, and therefore washing out cannot be effected.

2. That the drug causes increased katabolism of the tissues. But the increase is too great, and no marked loss of weight occurs on administration of salicylates such as this hypothesis would necessitate.

3. That it causes synthetic production of purins. This is not proven, but by a process of exclusion seems the only possible explanation. It would appear ironical if, in their enthusiasm for 'washing out' uric acid, those to whom it is anathema are merely increasing its production.

Atophan, or its English equivalent, *quinophan* or *phenoquin* (2. phenylchinolin, 4. carbonic acid), is another comparatively new phenol derivative which definitely increases the output of uric acid. When it is taken by a healthy individual, the excretion of uric acid even on a purin-free diet rises at once, and then slowly falls, returning to normal by the third or fourth day. When uric acid is injected into a normal man, its excretion is spread over several days, and the total amount injected is not recovered. But if the injection is given during a course of atophan, the excretion of uric acid is completed within twenty-

four hours, and the whole amount is recovered. In a gouty individual the same results are obtained (Walker Hall), so that under the influence of atophan the gouty and the healthy renal cell seem to excrete just the same amount of uric acid. Its administration appears to shorten the acute stage of gout, and is accompanied by increased uric acid output. So far as it goes, this might be held to support the retention theory. More probably, however, both retention and constitutional disturbances are due to the same unknown perversion of metabolism, and the drug affects the endogenous formation of purins. It is put up in tablets containing 7½ grains, 4 to 6 of which should be given in the day, broken up in plenty of water. Weintraud, who warmly recommends it, advises full doses of sodium bicarbonate at the same time, such as ½ ounce on the first day, and 1½ drachms on subsequent days. The method is well worth a trial both in acute and chronic gout. It is obviously contra-indicated in urinary calculus and gravel.

The use of *colchicum* in acute gout is purely empirical, but is undoubtedly often efficacious in the relief of pain. Dixon and Malden found that its active principle—colchicine—excited the nerve endings of plain muscle, and that the number of leucocytes diminished at first, afterwards returning in increased numbers. It is probable that the exciting effect on plain muscle is responsible for the purgative action of colchicine, which may serve to eliminate some gastro-intestinal toxin, while the diminution of leucocytes, by diminishing the

endogenous formation of uric acid at this juncture, may perhaps just tide over the metabolic difficulty. The return of the leucocytes in increased numbers would account for the failure of colchicum to exert a prolonged influence.

Prevention of Deposition of Uric Acid in Urine.—Though we can do comparatively little to increase the output of uric acid, we can and ought to check its deposit in the crystalline state in the urine, causing symptoms of stone and gravel. Sir William Roberts showed the importance of high acidity and high percentage in causing this deposit.

Acidity is at its height during the fasting hours, and seldom is a marked feature during digestion, owing to the loss of acid by the gastric juice. It is usually sufficient to give 20 grains of *potassium citrate* night and morning to correct high acidity. There is, however, one precaution which I have not seen mentioned, but which seems to me important. If uric acid deposit has already occurred in the form of a calculus, rendering the urine alkaline will cause growth of the calculus by accretion of phosphates. I therefore tell the patient to put a piece of red litmus-paper into the morning urine. If it turns blue, the drug must be diminished in amount until this just does not occur. *Fresh fruit,* such as pears, green figs, dates, oranges, and grapes, have been shown by Smith Jerome to have a similar action in checking high acidity. Fresh fruit, however, does not seem to suit the gouty subject with a large formation of endogenous purins.

High percentage of uric acid may be absolute or relative—that is, the total output may be increased or the urine may be concentrated. Both may favour deposition. The former should be regulated by cutting off foods rich in purins, the latter by diluting the urine. Patients do not care to be ordered to drink plain water. *Potash water* is preferable to soda water, because of the relative insolubility of the sodium salts. But, for the reasons I gave when considering the action of lithia, it is the water which is the chief therapeutic agent.

Certain waters, such as those of Contrexéville, have a high repute for washing out uric acid. It has been questioned, however, whether the treatment at Contrexéville does not increase the endogenous formation of uric acid; whether, in short, as Goodhart says, the gravel passed is not manufactured on the premises. But an alkaline mineral water will help to prevent deposit of gravel both by diluting the urine and by rendering it less acid.

Gee pointed out the extraordinary effect of *whey* in preventing uric acid deposits, and I have repeatedly confirmed this. I do not know whether the effect is due to its action as a diuretic, but there is no doubt as to the fact. A breakfastcupful should be given twice or thrice a day.

To sum up, uric acid is merely one, and one of the less toxic purin bodies. The purins come partly from the foods and partly from the tissues. The food purins are largely destroyed by the liver in health, giving

rise to urea. The tissue purins are increased by leucocytosis and muscular activity. Though we can control the intake of food purins, we have very little control over the tissue purins. For the ordinary individual, purins have hardly any toxic action. The gouty subject seems unable to metabolize his purins properly, and his kidneys excrete them too slowly. The inadequate metabolism leads to toxic symptoms, and the inadequate excretion to uratic deposit. It is still unknown what causes this inadequacy. Most of the drugs supposed to wash out uric acid from the system are incapable of doing so. Atophan and salicylates will definitely increase the excretion of uric acid, but it is doubtful whether they do not do so in part, at any rate, by increasing its production. It is reasonable to diminish the purin intake in individuals whose power of metabolizing purins is defective, but probably in many cases much of the good done is simply due to reducing the quantity of food eaten by making it monotonous. Deposit of uric acid in the urinary tract can be diminished or prevented by diluting the urine and rendering it less acid.

Estimation of the Urinary Purins.—The only method suitable for clinical work is Walker Hall's purinometer. It is easy to work, but gives only a very rough approximation. It has not proved of general utility.

CHAPTER VII

OXALURIA, PHOSPHATURIA, AND URINARY CALCULI

Oxalate crystals, phosphatic deposits, and albumen may each occur in the urine under varying conditions, in which they may have a widely different significance. Physiological considerations may help us rightly to appraise these, and may point out a line of rational treatment.

The Basis of Urinary Calculi.

Urinary calculi are mixtures of crystalloids and colloids. This fact seems to explain their comparative insolubility, since the colloidal precipitate, which forms an essential part, is 'irreversible'—*i.e.*, does not redissolve on being placed in non-saturated solutions. The ordinary colloids in the urine, such as urochrome and mucin, are reversible, but, according to Schade, in certain pathological, and especially inflammatory, conditions, fibrinogen or fibrin, typical irreversible colloids, appear. For him, then, an inflammatory reaction is a necessary precursor of a calculus.

Benjamin Moore (*British Medical Journal*, 1911,

i., p. 737), maintained that the discrepancy between the expected and actual solubility of calculi is due to a misconception as to their composition. This has generally been assumed from their appearance or from a partial and qualitative examination only. In this way the tradition has grown up that calculi are most commonly composed in the main of uric acid and urates. The striking murexide reaction is easily obtained if there be present only a small quantity of these substances. But complete quantitative examination of a series of twenty-four calculi removed by operation showed calcium oxalate to be the most frequent constituent of their centres. There were only two exceptions to this—namely, two stones, each removed from the bladder, which were almost purely uratic. This marked difference suggested to him that they were of an entirely independent origin, and had not been formed in the kidney at all. The comparative failure of the medical treatment of renal calculi he considered due to its being directed towards dissolving uric acid by alkalies, which could have no beneficial action on calcium oxalate crystals.

His observations have been confirmed by others, and form another useful warning against the tendency, so common in medicine, towards unquestioning acceptance of traditional statements, which are copied from one textbook into another. He went on to urge that it is of little consequence whether a degenerated kidney cell or micro-organism formed the nucleus around which

a renal calculus grows, or whether it starts spontaneously, since it is only a certain type of disordered metabolism, producing certain insoluble salts of calcium, which can keep it growing. This disordered metabolism he considered to be due to defective oxidation comparable to the calcification of cartilage and arteries in later life and the calcareous deposits in tuberculous foci, which are non-vascular. But he went too far in assuming a special relation between calcium and defective oxidation. The deposit of calcium salts tends to occur even in dead matter. Bodies buried in damp soil show it. The structural change occurs first, the deposit of calcium follows.

He laid curiously little stress on the fact that oxalates were the most abundant of the calcium salts in the majority of his cases, regarding this as merely due to their greater insolubility. The treatment he suggested was to diminish the intake of calcium salts by forbidding milk, things made with milk, wholemeal bread and oatmeal. But the conditions leading to an increased excretion of oxalates are also worthy of consideration, since they probably play as important a part in the formation of calculi as the base with which they are combined.

Oxaluria.

The urine contains substances which have been introduced with the food (exogenous) and substances which have been formed within the body (endogenous).

The origin of oxalates from the food is clear; their formation within the body is not so easily proved.

Small quantities of oxalates are normally present in urine, but they only have any clinical significance when they are deposited as calcium oxalate in envelope or, less commonly, dumb-bell crystals.

Sources of Urinary Oxalates—(a) Ingestion of Oxalates in the Food.—Rhubarb (which contains 0·24 per cent. of oxalic acid), spinach (0·32 per cent.), sorrel (0·36 per cent.), and strawberries, in my experience, are most prone to produce oxaluria in sufficient amount to cause symptoms. But many other articles of diet contain oxalates—*e.g.*, figs, potatoes, beetroot, French beans, tomatoes, plums, tea, coffee, and cocoa.

On the other hand, peas, asparagus, mushrooms, onions, lettuce, rice, cauliflower, pears, peaches, grapes, melons, wheat, and oats contain little or no oxalates.

Baldwin's *oxalate-free diet* is composed of meat, milk, eggs, sugar, butter, wheat-meal, rice, and biscuits.

The greater part of the oxalates in the food are in the form of the insoluble calcium oxalate. This can hardly be absorbed as such, but is decomposed by the acid of the gastric juice, which accordingly seems to influence the absorption of alimentary oxalates. Thus, if there is no hydrochloric acid in the gastric juice, there may be no oxalates in the urine, even if spinach be eaten; but on giving hydrochloric acid by the mouth oxalates will appear. Similiarly, we may reduce these alimentary oxalates by giving alkalies.

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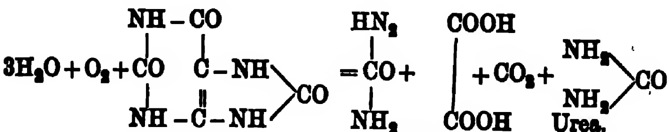
(*b*) *From Gastric Fermentation.—It is curious that oxalates will appear under precisely opposite conditions*—when there is no hydrochloric acid. But to produce them then, abundant fermentation of sugar must be going on in the stomach, producing oxalic acid. As the oxalates are formed in the gastric contents, this amounts to ingestion as the source of the oxaluria. Thus Baldwin produced oxaluria in dogs by feeding on meat and excess of dextrose. A mucous gastritis with absence of free hydrochloric acid resulted, and oxalic acid was found in the gastric contents. The organic acid here provided for its own absorption, As already pointed out, oxaluria may similarly result from chronic pancreatitis.

(*c*) *Endogenous Formation.*—In the laboratory decomposition of uric acid results in the formation of oxalic acid.



Uric acid. Urea. Oxalic acid. Urea.

A similar change has been assumed to occur in the body. Uric acid is extensively decomposed in the liver. If uric acid is perfused through an excised liver, oxalic acid is formed. If the metabolism of the liver is incomplete, it is easy to suppose the central carbon chain of the uric acid is not completely oxidized, when oxaluria would result.

However, several observers (Dunlop, Baldwin,

Rendle Short) have been unable to find any oxalates *in the urine on a milk diet, while others have found* traces. We may conclude that endogenous formation does not occur in sufficient quantity to produce a deposit of oxalates which is usually the result either of ingestion of food rich in oxalates or of fermentation in the stomach or duodenum, especially with excess of carbohydrate diet.

The body has considerable powers of dealing with oxalic acid. Esbach took as much as 6 grammes without inconvenience, and though it is almost certain that not all of this could have been absorbed, 0·181 gramme was found in the urine. Minkowski believes that, when once absorbed, oxalic acid does not undergo further oxidation. Maguire thinks that the unexcreted remainder in Esbach's experiment must have been deposited as calcium oxalate in the tissues.

Symptoms—(a) Urinary Irritation.—Most cases only show this. They are most frequent in the strawberry season, especially if the weather be very hot, so that the urine is also concentrated. I would suggest that there are several factors at work here. Strawberries contain oxalates, cream tends to dyspepsia, and the sugar by its fermentation produces more oxalates.

Micturition becomes painful, and is followed by prolonged smarting. Hæmaturia is not infrequent. Envelope crystals are found abundantly in the urine. I know men in whom such symptoms occur every summer, and one man in whom they occur every time he eats rhubarb.

Albuminuria is often associated with oxaluria, probably from mechanical irritation of the kidney by the calcium oxalate crystals. That actual hæmaturia occurs in the severer cases supports this idea.

(*b*) *Oxalate calculi* may form; they are hard mulberry-stones, usually mixed with uric acid.

(*c*) *Remoter Symptoms.*—It follows, from what I have said, that fermentative dyspepsia will lead to oxaluria. The so-called 'remoter symptoms' and the oxaluria must be referred to a common cause. We must not regard the oxaluria as causing them. The nervous symptoms do not resemble those seen in oxalic acid poisoning at all.

Such symptoms often occur in crises, sometimes precipitated by worry or overwork, sometimes by some intercurrent disorder. They consist of attacks of depression and lassitude, headache, smarting pains on micturition, and sometimes hæmaturia, neuralgic pains in the back, chiefly referred to the kidney. The patient often becomes hypochondriacal. This oxaluria is the index of a very low state of health (Gee). I may quote the following example:

A nervous, delicate, hard-working youth suffered from paroxysms of pain in the left side. Physical examination and a skiagram revealed nothing. The urine contained abundant crystals of calcium oxalate, but no albumen. The paroxysms generally came on if he overworked or took much muscular exertion; they left him fatigued and much depressed. Subsequently

he had two attacks of hæmaturia, the second rather severe, and accompanied by much pain. A stone was suspected, and his kidney was explored, but nothing was found to account for the symptoms. He had no more hæmaturia, but some occasional attacks of pain.

Treatment of Oxaluria.—The recognized treatment is abstention from oxalate-containing foods and administration of magnesia, since the oxalates are more soluble in the presence of magnesia. Peas should be taken when in season, as they are poor in oxalates and rich in magnesia. For Klemperer and Tritschler showed that when the amounts of CaO and MgO in the urine were about equal, as long as the urine contained 0·02 per cent. of magnesia, the calcium oxalate remained in solution, probably owing to the formation of a soluble double salt. And although the amount of oxalate deposited is no guide to the total oxalate excreted, it is only the deposit which causes the urinary symptoms.

Potassium citrate is of service in two ways—

1. As a diuretic it dilutes the urine.

2. By combining with the calcium it prevents the formation of calcium oxalate crystals. Martin showed that citrate threw calcium out of action by forming a non-ionizable soluble double salt. It is well known that citrate prevents the curdling of milk and the clotting of blood for this reason, and it has therefore been extensively used in the treatment of gastro-intestinal conditions.

I have employed it in oxaluria with success. Some observers prefer to employ lemon-juice to sodium or potassium citrate, and claim that in phlebitis, at any rate, it is much more effective. Now, if we can tell our patients that they need not give up strawberries altogether if they will also drink lemon squash, I believe we shall effect the desired object while avoiding irksome restrictions. A caution against much sugar while on this treatment should also be given.

An increase in urinary acidity will assist the solution of oxalate calculi, just as increased gastric acidity will assist the absorption of oxalates. Maguire has found the administration of acid sodium phosphate, in doses of up to an ounce a day dissolved in 100 ounces of distilled water, effective in diminishing the size of oxalate calculi. It is obviously important that there should be no ingestion of oxalates during this treatment, as the acid salt would facilitate their absorption.

In the nervous cases we must treat the digestive disturbance also, and direct attention to preventing fermentation of the sugar. A holiday and change of air is generally required.

Phosphaturia.

Normally phosphates are present in the urine as—

(*a*) Acid phosphates of sodium and potassium.

(*b*) Earthy phosphates of calcium and magnesium.

It is only the earthy phosphates that can form a deposit. This may occur—

1. In the bladder, so that the last portion of the urine is milky. This is often mistaken for spermatorrhœa; the patient becomes needlessly depressed, and falls an easy prey to quacks.

2. As an iridescent pellicle on the surface of the urine when it has been passed.

3. Only on boiling the urine, when acidification is necessary to prevent confusing it with albumen.

Calcium phosphate forms a deposit of stellar crystals, magnesium phosphate appears as rectangular plates with bevelled edges, while ammonio-magnesium phosphate ('triple phosphate') forms 'knife-rest' or 'coffin-lid' crystals.

The term 'phosphaturia' is somewhat loosely applied to any condition in which these various deposits occur. But it is clear that such deposit does not imply any increase in the total output of phosphates, since in no circumstances will the sodium and potassium phosphates be precipitated, while the earthy phosphates will be deposited on adding any alkali to any urine. Quantitative estimation would be necessary to prove an increase.

Usually phosphaturia is merely a sign of diminished acidity of the urine.

Now, if there be excessive secretion of hydrochloric acid in the gastric juice, the withdrawal of acid ions from the blood leaves less acid at the disposal of the urine during digestion. Phosphaturia is therefore common in hyperchlorhydria, even though a corresponding over-secretion of alkaline pancreatic

juice might have been expected to check its occurrence.

Many organic salts, such as citrates and tartrates, become bicarbonates in the blood, and thus reduce the acidity of the urine. Phosphaturia may therefore follow a diet rich in fruit and vegetables.

Again, if there be cystitis, ammoniacal decomposition will lead to a deposit of phosphates which will take the form of crystals of 'triple phosphates.' The occurrence of 'knife-rest' crystals at once suggests cystitis. In one case I saw, the passage of these crystals had occurred with hæmaturia at intervals for over a year. Between the attacks the urine was quite normal; but a stone was ultimately found. I have seen particularly copious deposits of triple phosphates in staphylococcal infections of the bladder.

There is, however, a residue of cases where the output is increased from the normal 2½ grammes of phosphoric acid to perhaps 7 or 9 grammes. Here the earthy phosphates will probably be in excess. The ratio of earthy to alkaline phosphates, which is normally 1 to 2, may rise to 5 to 2. It was formerly thought that this was due to excessive breaking-down of the phosphates of the brain, as it is common in neurasthenia, but there is no proof of this.

Wasting causes an increased excretion of phosphates, because the disintegration of nucleo-proteins yields phosphates. Conversely, phosphates are diminished in the urine in pregnancy and in convalescence after fevers, because they are required for building up.

Phosphaturia may, therefore, be merely a symptom of wasting. Sometimes no definite cause for the wasting can be found. Thus the editor of a 'hustling' journal, aged thirty-eight, consulted me for loss of weight (28 pounds in two months). He was suffering from depression and 'brain-fag,' but there was nothing objective except phosphaturia. Tonics and alteration in his mode of life led to great improvement. Again, a man, aged fifty-two, was sent to me to find a cause of his loss of flesh. He had formerly been in a business which had declined so much that he had recently taken up a new occupation which entailed much walking. Some swelling of the legs came on, and he became very thin. Except some old adhesions round his shoulder-joint, which explained the pain and limitation of movement he experienced there, I could find nothing beyond phosphaturia. As he gradually became accustomed to his new occupation, he put on flesh again under ordinary tonic treatment.

I have met with marked phosphaturia in cases of multiple myeloid tumours leading to albumosuria. No doubt this was in consequence of the earthy salts being set free by the destruction of the bones.

Phosphaturia may also occur in cases of marked depression without wasting. It was the only objective sign I could find in a young man who had recently gone into business on his own account, and who consulted me for paroxysms of fear of failure. It was present also in the case of a young man of the anxious, nervous type, who was on the Stock Exchange, and

consulted me for headache, insomnia, and impairment of memory.

Probably the phosphaturia in these cases is symptomatic of a diminished formation of acid due to a general depression of metabolism.

In Ralfe's opinion cases of phosphaturia with wasting are apt to go on to serious organic diseases if they do not rapidly yield to treatment, but I have only observed such a sequence once. A man, aged fifty years, had much anxiety on account of the prolonged and ultimately fatal illness of his wife. He was much frightened because his urine had an iridescent scum on it. I found it was composed of phosphates, the urine being scarcely acid. Two or three years later he developed chronic interstitial nephritis, and had an attack of cerebral hæmorrhage which left him aphasic. I do not think, however, that there was any connection between the phosphaturia and this event. More probably the prolonged anxiety caused both depressed metabolism and high tension.

Treatment.—We must remember that phosphaturia is a symptom and not a disease.

1. If triple phosphates be present, seek a cause for cystitis and treat that.

2. If phosphaturia depends on hyperchlorhydria, the digestive condition requires treatment.

3. If it be associated with wasting, the cause of the wasting calls for attention.

4. If it be a symptom of depressed metabolism, the patient is usually much benefited by giving him the acid he cannot make, preferably combined with tonics.

Now, phosphoric acid usually suits these patients well. If their symptoms were really due to phosphatic loss, this would hardly be the case, because there would already be excess of circulating phosphate, and the tissues could not discriminate between this and the administered phosphate. Moreover, on a fish diet, rich in phosphates but not acid, the phosphaturia will probably be aggravated. Therefore it is simply because it is acid that phosphoric acid does good, and in my experience it does not matter whether you give phosphoric or nitro-hydrochloric acid. But an inorganic acid should be given, and with it tincture of nux vomica.

If the deposit of phosphates makes the patient anxious, as it is apt to do, Soetbeer's method of diminishing the calcium intake may be used. Milk, eggs, fish, fruit, which contain a good deal of lime, are not allowed, while food poor in lime, such as meat, potatoes, and cereals, is given. The phosphates are then excreted in more soluble forms.

It is an interesting point of contrast that neurasthenics tend to oxaluria when the urine is very acid, but to phosphaturia if the urine is not very acid. It suggests a disturbance of calcium metabolism, the form in which the calcium salt is excreted depending on the reaction of the urine.

Cystinuria.

Cystin is only an occasional constituent of urinary calculus. Its presence in more than minute traces

appears to be due to an inborn error of metabolism (Garrod). It is an amino acid containing sulphur and is contained in many proteins, being especially abundant in hair. The tendency to deposit hexagonal crystals in the urine is lifelong in some persons, and runs in families, more commonly in the males. Exceptionally the deposit of crystals has occurred in the tissues, imitating gouty tophi. Cystinuria is little influenced by diet, and indeed the patient can usually deal with large quantities of cystin given by the mouth. It is the endogenous metabolism which is at fault, the sulphur containing fractions of the tissue proteins being excreted as cystin instead of being further decomposed. The excretion of cystin is often accompanied by a variable amount of diamines, such as putrescin and cadaverin, which are not normally present in the urine and probably originate in the same way from incomplete breakdown of the tissue proteins. A cystin calculus is yellow, turning green on prolonged exposure to light, somewhat translucent, with a crystalline surface, rather soft and friable in structure.

Cystinuria may continue for years without producing calculi, and indeed an additional factor appears to be required before this occurs. The additional factor is an infection of the pelvis of the kidney, very generally due to *B. coli*; then the inflammatory colloids are provided, which glue the crystals together into a calculus. To render the urine aseptic is therefore the first indication in the treatment of cystin calculi, in order to prevent increase in size. The only

other suggestion as to treatment is based on the hypothesis that endogenous cystin should normally become the taurin of the bile salts, and that its excretion as cystin is due to lack of cholalic acid with which it can conjugate. Cholalic acid may therefore be given in cystinuria as the prophylactic against calculus formation. On the other hand, alkalies help to dissolve cystin when formed, but cannot check the formation of fresh crystals.

The factors in the deposit of uric acid, the other important ingredient of a calculus, have been considered in the preceding chapter.

CHAPTER VIII

ALBUMINURIA AND THE TREATMENT OF NEPHRITIS

THE causes of true or renal albuminuria may be classified thus (Tirard):

1. Without definite structural change of renal tissue—
   (a) Mechanical—*e.g.*, from failing heart.
   (b) Hæmatogenous—*e.g.*, in the anæmias and in fevers.
   (c) 'Functional.'
2. With definite structural change of renal tissue.

'Functional' Albuminuria.

This has also been called alimentary, postural, cyclic, adolescent, to mention only a few of the names. Alimentary albuminuria is extremely difficult to produce. Certain experiments by D'Arcy Power upon himself are usually quoted as evidence of its existence. It is true that albumen appeared in his urine on the first day of the experiment, after twelve eggs had been eaten, but it disappeared in the evening, and did not reappear till the afternoon of the third day, after the

consumption of forty-eight eggs. It was found again during the evening of this day, after which it disappeared again, and had not reappeared at the end of the experiment, by which time sixty-five eggs had been taken. Only once was the albumen present in sufficient amount to enable its coagulation-point to be determined, so that there was very little connection between the number of eggs consumed and the amount of albumen. A significant point, which seems to have escaped notice, is that at this time D'Arcy Power was aged twenty-two, and that the occurrence of the albuminuria was always observed after a considerable amount of exercise had been taken. Now, transient albuminuria after severe exercise is common in young men, without excess of albuminous diet.

Collier found albumen present in the urine of every one of the Oxford crew of 1906 after rowing a course. In the case of half of them the amount of albumen was quite large, and in men who went in for running races the albuminuria was even more pronounced. In all these cases he found the urine passed in the early morning to be free from albumen. Such albuminuria may fairly be called 'physiological.'

'Functional' albuminuria without violent exercise is not an uncommon condition in males between puberty and marriage. Dukes found it in 16 per cent. of all the boys entering Rugby School at the ages of thirteen or fourteen. The strain of examinations seems to be a factor. A young man I knew who was working for an examination in physiology happened

to test his urine. To his alarm, it was loaded with albumen. He took a holiday, and the urine soon became free from albumen. Some years later the albumen returned during an intercurrent illness, again disappearing when he recovered from it. He is now a healthy man in busy practice.

The subjects of this condition are usually anæmic, weedy youths with a dull, heavy aspect, and a tendency to fainting. Dukes says that boys who faint in chapel are almost certain to be albuminurics. Their hearts are often excitable, and the condition vaguely diagnosed in them as 'weak heart' is frequently due to this.

Dukes divides them into three classes:

1. By far the largest class exhibit an increased arterial tension in consequence of irritability of the vasomotor nerves. The tension is, however, so unstable that it varies from hour to hour and day to day. This he regards as pathognomonic of the disease.

2. The next most extensive class comprises those who have cold, clammy, congested extremities, accompanied by a large, feeble, compressible pulse arising from deficient vasomotor control.

3. The remainder are the spare, highly-strung, oversensitive neurotics.

Cold bathing is another factor in inducing transient albuminuria, presumably by driving of blood from the periphery into the splanchnic area. The name proteinuria would be more exact, as a good deal of it is globulin.

In the cases where albumen readily occurs without some special strain hyaline casts may be seen, and often calcium oxalate crystals. Posture has an important influence. Albumen is absent from the urine passed first thing on rising, because this was secreted while recumbent; but it appears in urine secreted while in the upright position. With the fainting and the variable tension this strongly suggests a vasomotor element. A lax condition of the vasomotor system failing to compensate for the effect of gravity would allow both cerebral anæmia and back pressure on the kidney to occur.

Observations of the blood-pressure confirm this; whereas change of posture has an insignificant effect on the blood-pressure of a normal person, there may be a difference of 40 millimetres between the pressure in the upright and recumbent position in these patients. I have seen a case in a girl where there was a variation of 35 millimetres.

Edel, in eight cases of this condition, found a fall of pressure under conditions which ordinarily cause a rise in the healthy man. Coincidently with this fall, albumen appeared in the urine. Facts such as these place vasomotor insufficiency in an indisputable position as the principal factor in this form of albuminuria, to which the name 'orthostatic' may therefore fairly be applied.

Sir A. E. Wright believes that the coagulability of the blood is diminished in this condition, which would decrease its viscidity. Calcium salts increase both

coagulability and viscidity. He claims that calcium salts control functional albuminuria, whereas organic albuminuria is not diminished, and may be increased. The subjects of functional albuminuria have often been growing rapidly, so that there is an extra demand for calcium on the part of the tissues. He therefore considered the condition hæmatogenous in origin, and allied to a 'serous exudate,' such as occurs in urticaria.

Whether we accept this view of the pathology of the condition or not, it provides us with a convenient clinical test for functional albuminuria.

Fifteen grains of calcium lactate three times a day in water should control it. A possible fallacy is that the albumen often disappears spontaneously or is only present at certain times in the day. More systematic observations are required.

In six cases which I believed to be of this character the calcium lactate readily controlled the albumen, whereas in organic albuminuria I found it to have no effect as determined by Esbach's albuminometer.

Hingston Fox employed it in seven cases he thought were functional, and in all the albuminuria ceased, whereas in nine cases, apparently organic, albuminuria persisted.

While admitting this hæmatogenous element, we must not overlook the vasomotor element, which I believe to be of even greater importance.

Prognosis.—Dukes, who has probably had a unique experience of this condition, has entirely abandoned

his former opinion that it tended to organic kidney disease, for he has found that his patients even thirty years later were robust men. In fact, he has only found albumen subsequently in one of these cases, and that was in a boy who had only recently left school.

The question is one of great importance in connection with life insurance. At present the attitude of many offices towards albuminuria is one of total rejection or of heavy loading. Is this fair? I believe it is justified by some on the ground that the expectation of life is so much lower in albuminurics. Of course it is, if post-scarlatinal nephritis and other organic cases are included. They would naturally bring down the average. But has any attempt been made in such tables to exclude obviously organic cases? I believe not. Now that we have in calcium lactate a simply and readily applied test by which the functional can be discriminated from the organic, it seems to me that the rules of insurance companies and public services should be relaxed. It is not the duty of the medical man who examines for the companies or services to apply the test. Indeed, he has no business to treat as patients persons coming before him for examination. But the general practitioner can fortify his patient against the ordeal of examination by administering calcium lactate, and I can see no objection to his doing so; for he will not be able to secure the acceptance of sufferers from organic nephritis, but only of those who will almost certainly be free from albuminuria when adolescence is past.

Treatment.—Having assured ourselves by controlling the albuminuria with calcium lactate, by excluding the presence of casts other than hyaline, and by noting the effect of posture on the blood-pressure, that the case is one of orthostatic albuminuria, the first step in treatment is to reassure the patient. He usually comes before us, after the shock of rejection or postponement of his proposal for life insurance, believing himself to be the subject of an incurable disease, and is naturally apt to become hypochondriacal. Next a tonic line of treatment and a holiday are indicated, and usually that is all that is needed. I have used digitalis as well, and so far as I can judge the effect has been good, the general condition (such as the tendency to fainting) improving as well as the albuminuria ceasing.

Organic Albuminuria.

We must distinguish between a progressive nephritis and a leaky kidney, that has been damaged by old disease, but is not the seat of a progressive lesion. The ratio of albumen to globulin excreted, and the output of diastase in the urine will help us to do so, as shown in the following table (Mackenzie Wallis):

	Albumen.		*Globulin.*	*Diastase Output.*
Functional albuminuria ..	2	:	1	Normal
"Leaky kidney"	1	:	2	Normal
Chronic nephritis	6	:	1	Subnormal
Toxic nephritis (*e.g.*, mercurial poisoning, pregnancy	6	:	1	High

A nephritic kidney not only lets things pass out which it should retain, it also retains things which it should excrete.

Now the function of the kidney is to keep the composition of the blood constant. There are three factors—the urine, the kidney, and the blood; if any two of these are known, the third can be determined. Until lately the last of these has not been sufficiently taken into account. The problem is simplified by the fact that the kidney effects very little change in the material it excretes. Ambard pointed out that the kidney passes material into the urine in three ways: (1) Blood and lymph only appear when there is actual solution of continuity. (2) Alcohol, acetone, and the like escape by diffusion, without concentration occurring; (2) urea and other normal as well as some abnormal constituents are secreted in a higher concentration than that in which they are present in the blood.

Further, secreted substances fall into two categories: (*a*) Those which are purely waste products and useless to cellular life, such as urea, ammonia, and uric acid. There is no threshold for their excretion. Most drugs are apparently excreted in this way. (*b*) Those which may play a useful part in cellular life, such as sugar, sodium chloride, hæmoglobin, and water. The kidney interposes a threshold in the way of elimination of these, so that they only pass into the urine when their level in the blood exceeds this barrier. With the substances for which there is a threshold it is the height of that threshold which matters. For those without a threshold it is their concentration in the blood that counts. Ambard illustrates the position thus: the organism is a free-trader with regard to waste products, but a pro-

tectionist towards substances of value, imposing an export tax in proportion to their importance. He and others have attempted to draw a sharp distinction between hydræmic nephritis in which dropsy predominates, and azotæmic nephritis in which nitrogen retention is the important feature. In the former the output of the substances for which there is a threshold is disturbed. This includes salt, retention of which causes the œdema. In the latter it is the concentrating power of the kidney that is damaged. Though this distinction is helpful there are two difficulties in the way of its full acceptance. Cases of a mixed type are quite common; indeed, as Maclean admits, in the acute stage this is usually so. Secondly, retention of salt with its consequent raising of osmotic pressure of the tissues is not, as Widal thought, the only cause of dropsy in nephritis.

Epstein showed that a feature peculiar to chronic parenchymatous nephritis was a great reduction in the protein content of the blood which almost entirely affected the albumin and not the globulin. The daily drain on the protein may even amount to 10 per cent. of the total quantity in the blood. The osmotic pressure of the blood falls in consequence, giving the tissues the power to absorb and retain fluid. This tissue starvation is also shown by the high lipoid content of the blood, just as in advanced diabetes. That the blood serum may be milky in nephritis was noted by Bright, and subsequent observers have called attention to a similar condition in the ascites of this

disease. The lipæmia seems further to damage the kidney, while the abstraction of lipoids from tissue cells allows of imbibition of fluid, with consequent swelling of cells.

To sum up, salt retention and protein depletion with resulting dropsy and lipæmia are the principal features when the parenchyma of the kidney is diseased; nitrogen retention and cardio-vascular changes when its interstitial substance is involved.

The orthodox, conventional treatment of chronic nephritis has hitherto included the following principles:

1. Severe restriction of protein intake with exclusion of food rich in albumen, such as eggs; in bad cases absolute restriction to simple milk diet.

2. The estimation of the amount of urea in the urine is to be taken as a guide to the capacity of the kidney.

3. The kidney is stimulated to increased excretion by the use of diuretics.

4. Elimination by the skin is promoted by various diaphoretic measures.

I venture to assert that each of these principles contains, and, indeed, is based upon, a fundamental fallacy. In the light of recent work they require drastic revision.

I. Severe Restriction of Protein Intake.—When we proceed to limit the protein diet rigidly in Bright's disease, are we not led away by false analogies with glycosuria? Whereas there are the following essential differences:

(1) The sugar can be replaced by other things in a diet, while the protein cannot.

(2) The sugar excretion is preceded by an excess of sugar in the blood; albuminuria is not preceded by excess of albumen in the blood. The latter is due to a kidney lesion, the former is not.

(3) In Chapter V. it is pointed out that there is a great breaking-down of the protein molecule into its constituent groups before it is absorbed into the body. The simple conception of Liebig, according to which the protein food is simply hydrolyzed into peptone, and then assimilated into the tissues with no further change than dehydration, is no longer held.

It has been well said that, just as a Gothic cathedral could not be built out of a classical temple without reducing it to its constituent stones, so the protein of the tissues cannot be built out of the protein of the food without splitting it up into its simple constituent groups.

There is, therefore, no satisfactory proof that albumen is absorbed as such, and is able to run through the body; consequently, it is difficult to believe that the protein of the diet can directly influence the degree of albuminuria.

I have tested this point several times by estimating the albuminuria on varying diets and comparing it with the urea and total nitrogen excreted. I have found that the addition of three eggs to the diet did not really affect the albuminuria in cases of parenchymatous nephritis.

We know now the physiological minimum of protein

is much less than the 100 to 125 grammes formerly ordained. From observations on himself, his assistants, students, and a squad of soldiers, Chittenden concluded that weight and nitrogenous equilibrium could be kept up on 50 to 60 grammes protein a day or even less, with no diminution, but rather an increase, of physical or mental fitness.

A number of workers in one of the London physiological laboratories recently tested what amount of protein each was taking in the day; no alteration was made in their ordinary meals. With one exception, they were all taking less than the Voit standard, and one was taking only about 60 grammes. Thus a representative group of brain workers in this country tends to eat a very moderate amount of nitrogenous food, which may be taken to confirm Chittenden. He has certainly proved a point of great interest and importance—that the minimum protein requirements of the body are much less than was supposed. But he goes much further, and maintains that the minimum is also the optimum. To consume protein in excess of that required for the repair of the tissues he regards as a physiological sin, the wages of which is migraine in earlier and cardio-vascular degeneration in later life. He gives no evidence of this, but assumes that the nitrogenous excess overtaxes the kidneys by which it has to be excreted. Why he assumes that the kidneys are unable to do more than the minimum necessary without damage to themselves is hard to see. He might as well assert that the deeper breathing necessi-

tated by reasonable exercise dangerously overtaxes the capacity of the lung to excrete CO_2, and tends to asphyxia. He is, in fact, obsessed with the old idea that the body is unable to make any other use of protein food than to repair tissue waste—an idea which other lines of work have rendered improbable. The physiological minimum is not necessarily the physiological optimum. Experience goes to show that when there live, side by side, a race living on a protein-rich diet and one on a protein-poor diet, such as Europeans and natives in India, the morbidity and mortality of an epidemic are much higher in the latter. The rapid rise of Japan corresponds to the adoption of a more liberal nitrogenous diet. To this Chittenden answers that prosperity causes an individual or a race to elaborate the menu, that the increased food is not the cause of the improvement.

Of our protein diet very little is used for direct repair of tissue waste, but doubtless much of the rest is used as a source of energy, and it is at least probable that the ammonia groups set free from this protein excess are useful in neutralizing acids which might otherwise lead to acid intoxication; moreover, protein in moderate excess of minimum requirements gives the tissues a wider choice of building material from which to select. In Hutchison's phrase, protein is one of those things of which it is necessary to have too much in order to have enough.

II. Urea Estimations as a Guide to the Renal Capacity.—When we give a normal individual an

excess of protein food, he turns it into urea, and excretes it as quickly as possible. For this reason it seems to me that the amount of urea secreted in the day gives very little information as to the severity of a case of Bright's disease, unless the diet is carefully taken into consideration.

The procedure often adopted is irrational. A man with chronic nephritis on a restricted diet has his urea estimated. Instead of the normal 30 grammes, he is found to be passing, say, only 16. The physician concludes that the capacity for urea excretion must be seriously decreased; the patient must take less nitrogenous food. This is done, and the next analysis shows an even lower urea excretion. 'Worse and worse,' thinks the physician; 'this man is only fit for a milk diet.' Accordingly he is given three pints of milk a day and nothing else. He now bids fair to fulfil the gloomy prognosis formed, unless he fortunately rebels against this pitiful fare, and takes the law into his own hands. For, as the greater part of the urea comes direct from the food, the more the nitrogenous food is restricted the less urea will be excreted.

Of course, a patient on the diet ordinarily given in nephritis passes less urea than normal, because he is given a diet poor in protein. But the output probably will not be so little as that of a healthy fasting man, while it will certainly be more than that of a man on Folin's diet of starch and cream, in which the nitrogenous excretion is reduced to a minimum, because

so much of the energy is derived from sources other than protein.

What the physician expects to learn from the urea estimation without reference to the amount of nitrogen in the food is hard to say. If he knew the total nitrogen excreted, as estimated by Kjeldahl's method, he could see whether the body was converting a due proportion of the nitrogen into urea; this would give him some information as to the capacity of the individual, but urea estimations by themselves tell him practically nothing. This fallacy vitiates many of the conclusions arrived at by so careful an observer as the late Professor Foxwell (*Lancet*, 1908, vol. ii., p. 1425). He hardly mentions the diet factor at all. In one case he certainly says that he found a patient with chronic nephritis passing as much as 585 grains (39 grammes) of urea a day. On inquiry, he learned that the patient, feeling run down, was taking six meals a day, three of them being good meat meals. This shows that a chronic nephritic may excrete even more than a healthy man does on his ordinary diet, though it presumably taxes his kidneys more. We can agree with Professor Foxwell that a daily output of 250 grains of urea is the lowest on which a man can permanently exist without losing ground; for this would represent a daily intake of about 50 grammes of protein, which is little enough to satisfy even the most extreme 'nitrogen economist.' In short, the amount of urea excreted by the kidney is largely determined by the amount of protein eaten, and, within wide limits, on little else.

What is the bearing of all this on the treatment of chronic nephritis?

It will be of material assistance to know the amount of urea in the blood. This should normally lie between 15 and 50 milligrammes per cent., although the latter figure would be rather high before middle life. If the blood contains no excess of urea, we can safely permit a much greater variety in the diet than is allowed on orthodox lines. We should naturally avoid meat extracts and cellular foods, such as sweetbread, because they contain a large proportion of purins, which have to be excreted by the kidney, and this, when damaged, has difficulty in dealing with uric acid at any rate. If there is dropsy, the intake of salt should be greatly restricted. Indeed, as Bryant found, even a healthy man with a healthy heart and kidneys may develop œdema as the result of taking excess of salt. The substitution of lemon-juice will usually satisfy the patient. The amount of fat should also be cut down as much as possible.

But Epstein would go much further than this. He would give a liberal protein diet in such cases in order to make good the drainage of albumin into the urine. His diet is selected from the following: lean veal, lean ham, whites of eggs, oysters, gelatine, Lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, tea and cocoa. He gives 120 to 240 grammes of protein, 20 to 40 of fat (unavoidably present in other foods), and 150 to 300 grammes of carbohydrate; with this 1,200 to 1,500 c.c.

of fluid and enough salt to make the food palatable are allowed.

At St. Bartholomew's Hospital the following simple modified diet to fulfil Epstein's indications has been used with benefit in suitable cases:

MODIFIED EPSTEIN DIET.

Solids.	*Fluids.*
Breakfast:	
Egg, 1, boiled or poached.	Tea, 250 c.c.
Bread.	Milk, 25 c.c.
Jam.	Sugar, *q.s.*
Lunch:	
Bread and jam.	Tea, 250 c.c.
	Milk, 25 c.c.
	Sugar, *q.s.*
Dinner:	
Lean meat, 50 grammes to 100 grammes.	Lemonade, 250 c.c.
Potato.	
Greens.	
Fruit.	
Tea:	
Egg, 1, boiled or poached.	Tea, 250 c.c.
Bread.	Milk, 25 c.c.
Jam.	Sugar, *q.s.*
Supper:	
Lean meat, 50 to 100 grammes.	Lemonade, 250 c.c.
Bread.	
Tomato.	

Three times a day and once during night: Lemonade or Water, 250 c.c.

Although not prepared to agree with all Epstein's conclusions, I am convinced that he is right in saying that a salt-free diet is not always successful in abolishing œdema. I would agree with him that a diet rich in protein is sometimes more successful. I am inclined, however, to think that the disappearance

of œdema may be due to the diuretic effect of the urea to which this diet gives rise as much as to its increasing the blood proteins, since, as I have shown, there is no evidence that one can directly increase these by food proteins. And again, the œdema of acute nephritis can hardly be due to reduction of blood protein, since it comes on at a time when the total volume of the urine is too small to have affected this seriously.

Maclean has introduced a urea concentration test, which is free from the objection I have raised to urea estimations in general. Fifteen grammes of urea dissolved in 100 c.c. of water and flavoured with a little tincture of orange are given to a patient first thing in the morning just after he has emptied his bladder. The urea in the urine passed one and two hours afterwards is estimated by the hypobromite method. If this amounts to 2 per cent. or more in the first specimen the kidney is efficient in concentrating power. But sometimes the diuretic action of the urea leads to dilution of the urine. As this will have passed off by the end of the first hour, the second specimen will act as a control. A moderately efficient kidney may show 1·5 per cent. and a bad one 1 per cent., or even less. Later observers have adopted rather higher figures, and advocate examination of a specimen at the end of the third hour. I am therefore prepared to accept the figures at the end of the second and third hours as most reliable. I do not employ this test when I suspect serious nitrogen

retention, and in the mixed type of case I prefer to have the urea estimated in the blood before trying it. Subject to these limitations it is a useful test, and

1. LOW NITROGEN DIET.

Solids.		*Fluids.*	
Breakfast:			
Milk ..	.. 4 ounces	Coffee ..	.. 10 ounces
Porridge ..	.. 8 ,,	Milk ..	.. 2½ ,,
Bread ..	.. 2 ,,		
Butter ..	.. ¼ ounce		
Lunch:			
Bread ..	.. 3 ounces	Milk ..	.. 5 ounces
Butter ..	.. ½ ounce	Barley water	.. 10 ,,
Lettuce or tomato	1½ ounces		
Dinner:			
Potato ..	.. 4 ounces	Lemonade, Imperial drink, or barley water ..	.. 12 ounces
Greens ..	.. 5 ,,		
Butter ..	.. ¼ ounce		
Stewed fruit	.. 4 ounces		
Boiled rice	.. 4 ,,		
Tea:			
Bread ..	.. 3 ounces	Weak tea	.. 10 ounces
Butter ..	.. ½ ounce	Milk ..	.. 2½ ,,
Lettuce or tomato	.. 1½ ounces		
Supper:			
Potato ..	.. 4 ounces	Lemonade or barley-water	.. 12 ounces
Butter ..	.. ¼ ounce		
Greens	.. 5 ounces		
Stewed fruit	.. 4 ,,		

This contains:—

Protein	43 grams.
Carbohydrate	283 ,,
Fat	50 ,,
Calorie value	1815

when it shows that the concentrating power of the kidney is good, I give 45 to 60 grains of urea three times a day in dropsical nephritis while the patient

is on a diet which is not excessive in proteins, but is poor in fats.

When urea retention is present, an excessive protein diet is inadvisable, even if the patient can metabolize

2. MODERATE NITROGEN DIET.

	Solids.		*Fluids.*	
Breakfast:				
Egg	1	ounce	As No. 1.	
Bread	2	ounces		
Butter	½	ounce		
Lunch:				
Bread	4	ounces	As No. 1.	
Butter	½	ounce		
Tomato or lettuce	1	"		
Dinner:				
Mutton or fish	3	ounces	As No. 1.	
Bread (alternate days)	2	"		
Butter	½	ounce		
Stewed fruit	4	ounces		
Tea:				
Bread	4	ounces	As No. 1.	
Butter	½	ounce		
Tomato or lettuce	1	"		
Supper:				
Greens	2	ounces	Milk	5 ounces
Potato	3	"		
Bread	4	"		
Butter	½	ounce		
Stewed fruit	4	ounces		

This contains (on average):

Protein	95 grams.
Carbohydrate	365 "
Fat	92 "
Calorie value	2,690

it, because he is getting the energy in a form that throws work on to the damaged excretory organs. What is the happy mean? I would suggest that we can arrive at it thus:

Chittenden's diet gives us the physiological minimum of protein. As the amount of protein in the diet has no appreciable effect on the amount of albumen in the urine, a patient with nephritis would not be able to maintain his nitrogenous equilibrium on Chittenden's diet. We must add an amount of protein equal to the albumen lost in the urine,* when we shall be giving just enough to maintain equilibrium and yet not be taxing the kidney by calling upon it for any unnecessary work.

Von Noorden finds, clinically, that the chronic nephritic can easily excrete up to 15 grammes of nitrogen in the day, but above this elimination becomes irregular and uncertain. Fifteen grammes of nitrogen corresponds to 94 grammes of protein, and this is the maximum that should be allowed, while the minimum is about 60 plus the amount of albumen in the urine. Thus the theoretical and clinical results agree fairly closely.

In the epidemic of war nephritis I found the diets on pages 240 and 241 useful. The low nitrogen diet is for cases with nitrogen retention, while the moderate nitrogen diet is for the convalescent stage.

The rules which guide us in acute nephritis or in

* A convenient rule is this: When the reading of the albuminometer is 5 and the amount of urine is 2 pints, the patient is excreting as much protein as is contained in one egg. I take these figures because they admit of simple proportional calculation, and also because they represent the amount of albumen excreted in a case of chronic parenchymatous nephritis of average severity—*i.e.*, 6 grammes, which is the amount of protein in one egg.

exacerbations of chronic nephritis are somewhat different, however. 'In acute affections we concentrate our attention on the diseased organ, whilst in chronic cases we keep the general condition of the patient more in view' (von Noorden). Nitrogen retention is a very prominent feature of acute nephritis, and a diet poor in nitrogen is strongly indicated. This period of retention is usually short; if it continues, it is very ominous. A few days' comparative nitrogen starvation will do no harm, and may avoid grave danger.

Von Noorden is of opinion that in acute and dangerous cases this is very necessary, and gives nothing but sugar, water, and fruit-juice for from three to eight days.

III. The Use of Diuretics in Bright's Disease.—There has always been a tendency to regard 'flushing out' the kidney as a good line of treatment in Bright's disease; but before employing it we should consider what method of diuresis we mean to employ, how far such methods are desirable in the case before us, and how far they will achieve the end desired. Routine and indiscriminate 'flushing out' is to be deprecated.

Methods of producing Diuresis.—The following are possible:

1. *By vaso-dilatation in the kidney*, as by the caffein group of drugs. These probably act as direct stimulants to the renal epithelium, the vascular change being secondary.

2. *By vaso-constriction elsewhere*, in consequence of which the blood-pressure is raised and more blood is

forced through the kidneys; digitalis has generally been held to act in this way, though this is doubtful.

3. *Increase in quantity of circulating fluid*—(*a*) by absorption of water from the intestine, as by giving the patient large quantities of fluid to drink; (*b*) by increasing the osmotic pressure of the blood. The saline diuretics, citrates, acetates, etc., act in this way, attracting water from the tissues into the blood-stream.

How far are these methods desirable in nephritis?

1. Why stimulate a damaged structure? I believe I have seen caffein, theobromine, theocin, and diuretin all produce bad effects. It is chiefly in chronic parenchymatous nephritis that one sees them employed, and there is a danger that they will cause a return of acute symptoms; hæmaturia not infrequently follows.

I have gradually come to the conclusion that this group of drugs is unsuitable for nephritis, and should be restricted to cases where diuresis is required and the kidneys are not organically diseased.

2. Accepting the modern view that digitalis is not a vaso-constrictor in man, it is difficult to see how it could be a satisfactory diuretic in cases of nephritis, except when there is cardiac insufficiency as well.

3. In acute nephritis it is really no good to give large quantities of water with the idea of flushing the kidney, for the kidney cannot excrete it, so that it accumulates in the tissues, increasing the œdema.

The importance of this defective adjustment of the

kidneys to varying water-supply is shown by the following observation of von Noorden's: A normal individual, with an average hourly diuresis of 52 c.c., excreted an average of 723 c.c. for three hours after drinking 1,800 c.c. of Salvator water; under the same conditions a patient with acute nephritis, excreting 91 c.c. hourly before, only passed 103 c.c. after. Spontaneous diuresis is the first and surest sign of convalescence.

The attempt to increase the urinary flow by increasing the osmosis into the blood is less open to objection in acute nephritis. Citrate of potassium renders the urine less acid and, therefore, less irritating to the kidney. As the extra water is drawn from the tissues it will tend to diminish, and cannot increase, the œdema.

I would put it in this way:

(*a*) *In acute nephritis* we cannot flush out the kidney, because the inflamed organ will not respond. I believe that potassium citrate is the best drug, because it does not irritate the kidney, and any diuretic effect it may have is at the expense of the œdema.

(*b*) *In chronic parenchymatous nephritis* the kidney is more responsive, but it is undesirable to increase its secretion, either by irritating it by caffein and the like, or by increasing the already raised pressure. I am inclined to make an occasional exception in favour of theocin-sodium acetate, in small doses, such as 2 grains twice a day. It appears to increase the permeability of the kidney, and, although allied to caffein,

is not so liable to irritate the kidney if given in these doses. But it should only be used to tide over an emergency, and is not altogether free from risk. The saline diuretics seem to be free from objection. In addition to potassium citrate I have given, with apparent benefit, 15 minims of liq. ferri acetat., and 2 drachms of liq. ammon. acetat., made up with camphor water. Urea may be useful when the power of the kidney to excrete it is good.

(*c*) *In chronic interstitial nephritis* the kidney responds quickly to altered intake of water. But some years ago von Noorden claimed that, rather than trying to flush out the kidney, it was desirable to restrict the fluids to 1½ litres a day. He maintained that this did not diminish the urea excretion, while the work of the heart was spared. He considered that the polyuria was secondary to polydipsia. To a limited extent this is true, but the kidney has lost the power of excreting a concentrated urine, so the restriction must be carried out with caution.

IV. Elimination by the Skin.—This method of treatment is open to the following objections:

(*a*) Only 3 grammes of nitrogen can be got rid of through the skin in the day compared with 8 grammes that can be more easily eliminated by the bowel.

(*b*) Physiological rest for the kidney is not secured by giving it a highly concentrated urine to deal with, for defective adjustment of the kidney to varying concentration of the urine is a prominent feature of azotæmic nephritis.

(*c*) Diaphoresis is an exhausting process and may depress the heart.

(*d*) The withdrawal of so much fluid without a corresponding removal of organic solids must increase the concentration of the toxins in the circulation.

If, therefore, it is decided to employ diaphoretic measures, it should be after fully weighing these objections as applied to the particular case. It has been urged in support of this method of treatment that, after a hot-air bath, the patient may be actually covered over with small crystals. These crystals, however, in the main, do not consist of urea but of sodium chloride; and here we have the clue to the kind of case in which diaphoresis will be of service—namely, that in which there is a defect in the elimination of sodium chloride with consequent œdema, for the retained salt increases the osmotic pressure of the tissues, and this tends to increase œdema and to diminish excretion. The elimination of salt by the skin may therefore be of indirect service by breaking a vicious circle. In a case of this sort I have actually seen diaphoresis followed by diuresis, which can only be explained in this way. I conclude that the hot-air bath is only suitable when dropsy is present.

It may fairly be objected that I have attempted to destroy the basis for treatment, without being able to put anything in its place; to a certain extent, this is true. The kidney, once damaged by chronic nephritis, cannot recover, and the only thing which can be done is to attune the mode of life to a low key, subjecting

the patient to as little strain as possible. He must be warmly clad and the kidneys protected from fluctuations of temperature as far as possible. The bowels must be kept freely open, as the best alternative route for elimination of toxins. He may have a considerable variety of food, provided that the intake of protein does not fall below 60 or rise above 90 grammes in the day, and provided that he takes very little purins and salt. In constructing the dietary it will be convenient to remember that a pint of milk, one egg, a ¼ pound of fish, and 2 ounces of meat contain altogether 72 grammes of protein. Allowing for the protein in bread and vegetables, it will be seen that the amount of nitrogen in this diet errs rather on the side of liberality. It will, however, serve as a rough guide. He can be helped by saline diuretics and unirritating preparations of iron. He will do all the better if his medical man realizes that many of the methods recommended in the treatment of this disease are impotent where not actually harmful.

Uræmia.

Uræmia is merely a clinical term to designate the final failure of the kidney to discharge its duties. No one to-day regards this as merely due to retention of urea. It is rather that renal failure alters metabolism so that abnormal toxic products are formed. While this is true in the main, not all uræmic symptoms can thus be explained. The vomiting and diarrhœa certainly appear to be attempts at vicarious

elimination of toxins which the diseased kidney cannot accomplish. The rashes and intense pruritus which sometimes occur are probably symptomatic of an attempt to excrete toxins by the skin.

It is true that there may be urea retention in uræmia, and Canti has shown that its degree is a measure of the prognosis. But if the hypobromite method is used this will evolve nitrogen from other substances besides urea. The urease method, on the other hand, only splits up urea. The difference between the two methods gives the amount of non-protein nitrogen other than urea. These figures from a case of mine are striking and typical. The cerebro-spinal fluid yielded 0·69 per cent. by the hypobromite method and 0·45 per cent. by the urease method. The amount of 'unknown nitrogen' was therefore greatly raised both proportionately and absolutely, being 0·24 per cent. Expressed proportionately it was nearly 35 per cent. of the total instead of the normal 8 per cent. In my opinion this unknown nitrogen is the real toxic element. Still the nitrogen yield by the hypobromite method from the blood or cerebro-spinal fluid gives a convenient index of nitrogen retention. When this, calculated as urea, is above 200 milligrammes per cent., there is serious nitrogen retention, and Canti found that 300 milligrammes or more was always a fatal portent.

On analyzing the chief symptoms other than diarrhœa and vomiting which have been attributed to uræmia, we find that they have different meanings.

(1) *Epileptiform Convulsions and Amaurosis.*—The most dramatic manifestation—namely, epileptiform convulsions—may develop, and recovery is possible not only from the uræmia, but from the nephritis. This has not been my experience with uræmic manifestations other than those in this group, which suggests that the toxins are not the same. Similar convulsions occur in eclampsia, which may also come on very suddenly, and from which recovery may be complete. Moreover, they occur in toxæmic kidney, in which the tubules are suffering from a degenerative but not an inflammatory change, the result of a chemical poison like mercurial salts or cantharides or the toxæmia of pregnancy. Although severely damaged for a time, such a kidney is, nevertheless, capable of complete recovery. It does not retain toxins, but is characterized by an undue permeability to anything which the blood presents to it (Mackenzie Wallis).

Amaurosis may occur under similar conditions—*i.e.*, acute nephritis, toxæmic kidney, and eclampsia—and is also capable of complete recovery. I am therefore inclined to attribute both symptoms to the same cause. And that cause is not retention of nitrogen, nor, as far as I know, of any other toxin. I believe that the toxin, whatever it may be, although it is not retained, damages the liver, part of whose work is detoxication. Venesection appears to be the best treatment.

(2) *Paroxysmal Dyspnœa (or Uræmic Asthma).*—It

has been established that acidæmia may occur in nephritis from the failure of the kidney to excrete acid sodium phosphate. In health the kidney and the lung can insure between them a fairly constant hydrogen-ion concentration in the blood; any change is soon compensated for. But when the kidney fails to excrete acid sodium phosphate the hydrogen-ion concentration of the blood must rise, and the respiratory centre will be stimulated to compensate for this by washing out more CO_2 from the lungs by increased respiratory effort. Yet even the marked dyspnœa which constitutes uræmic asthma may prove inadequate to compensate for the acidæmia. The heart muscle is poisoned, cardiac dilatation ensues, and pulmonary œdema follows. It is true that heart failure often excites dyspnœa in nephritis without acidæmia. But I would restrict the term 'uræmic asthma' to paroxysmal dyspnœa in nephritis before signs of heart failure develops. Here I will merely say that bicarbonate of soda should be freely given to increase the alkali reserve.

(3) *Headache, drowsiness, coma, hemiplegia, apoplectiform seizures, insomnia, and acute mental changes* usually occur in chronic lesions of the kidney, although they sometimes manifest themselves with great rapidity. This group of symptoms appears to be chiefly associated with kidney lesions when vascular changes are paramount. The association between chronic interstitial nephritis and cerebral hæmorrhage has been attributed to the occurrence of similar changes

in the vessels of the kidney and the brain. But the association between vascular changes in these two organs is not limited to cerebral hæmorrhage. The endothelium of the healthy cerebral vessels is extraordinarily impermeable to toxins. We can see how the active inflammatory changes of chronic interstitial nephritis which Geoffrey Evans has described must seriously diminish the impermeability of the cerebral vessels to toxins, and it is to this that a large part of the poisoning of the brain must be referred. Frequently, however, actual vascular lesions, such as punctiform or grosser hæmorrhages, are found in the brain, post mortem, when clinically the case appeared to be one of uræmia. Here elimination of toxins by every practicable channel must be tried. In such cases nitrogen retention undoubtedly plays an important part in the eventual disaster, but it is quite possible, as Canti has shown, for the cardio-vascular changes to lead to heart failure without serious nitrogen retention. Then treatment directed towards combating this heart failure is the only thing which is of any avail, and it is capable of producing remarkable temporary benefit.

The clear-cut features of the different types are often blurred by the co-existence of several lesions. Thus, suppression of urine following retention of prostatic origin is very likely to be complicated by vascular changes as well, considering the age at which prostatic troubles occur, while the septic complications to which nephritics are so prone are apt to

precipitate and to alter the manifestations of uræmia at any age.

It would appear, therefore, that even using the term in a restricted sense, the uræmic syndrome may be due to at least two different chemical substances, one nitrogenous and the other non-nitrogenous, in addition to vascular lesions and septic complications.

CHAPTER IX

GLYCOSURIA AND DIABETES

A MEDICAL man is often faced with the problem of deciding whether a patient is suffering from diabetes when his urine reduces Fehling's solution.

Certain substances other than sugar might be responsible for the reduction.

1. Uric acid and kreatinin may both cause reduction, and are normal constituents of urine. But they are never present in sufficient amounts to cause reduction, if we are careful to add only as much urine as we have taken of Fehling's solution.

2. Glycuronic acid is closely related chemically to dextrose, as is seen by comparing their formulæ:

$$\begin{array}{c} COH \\ | \\ (CHOH)_4 \\ | \\ COOH \\ \text{Glycuronic acid.} \end{array} \qquad\qquad \begin{array}{c} COH \\ | \\ (CHOH)_4 \\ | \\ CH_2OH \\ \text{Dextrose.} \end{array}$$

The reason for its appearance in the urine would appear to be that it has combined, like sulphuric acid, with putrefactive bodies or else with administered drugs, such as chloral, morphia, camphor, chloroform,

antipyrin, antifebrin, or pyramidon. Its function in this connection would appear to be antidotal, the conjugated acid being harmless. In this way protection against certain toxic substances is obtained.

Glycuronic acid may be present in fresh urine without causing any reduction, when, of course, confusion will not arise. Boiling for some time with 5 per cent. sulphuric acid will render it strongly reducing, however. Should a reduction be given with the untreated urine, glycuronic acid can be distinguished from dextrose by its failure to ferment. If it is found in the urine of a patient not known to be taking one of the drugs mentioned above, the test for indican should be tried, for it may simply be due to an unusual absorption of putrefactive bodies which are thus rendered inert. But if indican is not found, the suspicion of drug habits on the part of the patient may justifiably be entertained.

3. Alkaptonuria may be responsible. This 'is not the manifestation of a disease, but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong' (Garrod). The individual appears to be incapable of breaking down the tyrosin in the protein molecule completely, so that the intermediate product, homogentisic acid, appears in the urine. But the urine does not ferment, and it darkens on standing, or at once, on the addition of alkalis. It may stain the linen brown. When a dilute solution of ferric chloride is allowed to fall, drop by drop, into the urine, each drop produces a transi-

tory deep blue colour. Ochronosis—blackening of the cartilages and ligaments, and sometimes of the conjunctivæ—may occur. Usually there is a chronic arthritis also, which may lead to a curious 'goose gait.'

Other sugars than dextrose may be the cause of the reduction.

(*a*) Lactose is often present in the urine during and on the sudden cessation of lactation, and occasionally during pregnancy. Any lactose reabsorbed from the mammary gland cannot be utilized by the tissues because it is a disaccharide, and all carbohydrates must be broken up in the intestines into monosaccharides before they can be assimilated. But alimentary lactosuria is also very easily produced in women who are suckling, showing that their capacity for metabolizing lactose is physiologically depressed.

(*b*) Pentose exceptionally occurs in the urine. Its presence is due to a congenital incapacity to metabolize the pentose sugars set free in the breakdown of nucleo-protein. It may not reduce until the urine has been boiled for a few minutes, when the reduction takes place suddenly. It does not ferment, and may be further identified by the green colour it gives with orcin and hydrochloric acid. It is not a manifestation of disease.

(*c*) Lævulose may be present as well as dextrose in alimentary glycosuria. Alimentary lævulosuria can be easily excited in diseases of the liver, the diagnostic value of which has been discussed.

When equal parts of hot urine and hot Fehling's

solution are mixed and yield an orange precipitate *without reboiling*, it is almost conclusive evidence of the presence of dextrose or lævulose (Garrod). Benedict's test in which 8 drops of urine are added to 5 c.c. of his solution and boiled for two minutes is more sensitive and less open to fallacy. If the solution remains clear there is less than 0·1 per cent. of sugar; a green opalescence or precipitate means 0·1 to 0·5 per cent. of sugar, a yellow precipitate 0·5 to 2 per cent., while a red precipitate indicates more than 2 per cent. If it be desired to prove beyond a doubt that the reduction is due to dextrose, crystals of dextrosazone can be prepared by heating 10 c.c. of the urine with enough phenyl-hydrazone to cover a sixpence and the similar amount of sodium acetate. The reducing substance can also be removed by fermentation with yeast.

A normal man can deal with ingested sugar in the following ways:

1. He can store it as glycogen.
2. He can store it as fat.
3. He can use it at once for muscular energy.
4. Any excess that cannot be dealt with in these ways will pass out into the urine. Anyone will have glycosuria after taking enough *sugar* at one time. The limit of this assimilation for dextrose or cane-sugar is 150-200 grammes, lævulose is 150 grammes, and lactose is 120 grammes. This may be considered to be 'physiological glycosuria.' But glycosuria after any quantity of *starch* is not physiological. In Naunyn's phrase, a

patient who passes sugar after the free ingestion of starch is virtually a diabetic.

Even in patients who do not ordinarily pass sugar there may be a lowered tolerance for carbohydrates, which may precede the glycosuria and outlast it. As the kidney is capable of altering its threshold for the excretion of sugar, estimation of the urine alone does not give us full information as to the metabolic condition. For this purpose it is necessary to estimate the sugar in the blood, which has become even more important since the introduction of insulin.

It will be helpful to consider the ways in which glycosuria may be experimentally produced, with the clinical counterpart of each.

1. *Phloridzin Poisoning.*—Phloridzin produces glycosuria by its action on the kidney tubules, for if injected into one renal artery the glycosuria occurs sooner, and to a more marked degree, on that side; consequently, there is no excess of sugar in the blood, but rather a deficiency. At first no clinical equivalent of this was known, but now glycosuria with less sugar in the blood than normal is well recognized. The excretion of sugar generally lies between 1 and 2 per cent., and is very little influenced by diet. There are no symptoms, and the prognosis is more favourable than in ordinary glycosuria. The condition has been called 'renal glycosuria,' and it has been compared to that produced by phloridzin. To recognize it the response of the blood to 50 grammes of dextrose must be determined. A single estimation showing hypoglycæmia is not sufficient.

2. *Excision of the Pancreas.*—Lancereaux was the first to maintain the association of pancreatic disease with diabetes. Intralobular fibrosis is the most common change to find in the pancreas in severe diabetes. The pancreas may be the site of malignant or cystic disease without diabetes. There must be a more extensive destruction of the cell-islets than usually occurs under such conditions.

Rose Bradford has recorded a case where a large pancreatic tumour was seen at an exploratory laparotomy; three years later the patient was found to be suffering from severe diabetes, and the tumour could no longer be detected. I have had a case illustrating the converse condition. A woman who had been admitted for diabetes returned three years later with all the signs of obstruction of the common bile-duct and the pancreatic duct. As she was sixty years of age, I suspected new growth of the head of the pancreas, but under treatment the obstruction disappeared, though the glycosuria persisted. Such cases suggest that diabetes may have a pancreatic origin, even though there is no evidence of disease of the gland at the time the glycosuria is observed. Systematic use of the tests for pancreatic insufficiency may in future enable more of such cases to be recognized (see also Chapter IV.). As Allen puts it, there may be small scars showing that 'a storm has passed over the islands.'

But whether it is always a structural change in the pancreatic cell-islets that causes diabetes may

be doubted; certainly a secretory failure of them results.

3. *Adrenal Glycosuria.*—Injections of adrenalin are known to excite glycosuria, as when the drug is used for asthma. The chromaffin system, of which the adrenals are the most important part, seems to be antagonistic to the pancreas in regard to sugar metabolism. But this antagonism is expressed in its action on the liver, the glycogen stores of which it empties. Loewi's adrenalin eye-test for pancreatic disease, already described, is based on this antagonism, and may help in determining whether a given case of diabetes is pancreatic in origin.

It has often occurred to me that chronic over-action of the adrenals may afford a possible explanation of the frequent association of glycosuria with high tension in men in later middle life; for both these can be produced by excess of adrenalin. The influence of the nervous system in inducing this will be referred to later.

4. *Thyroid Glycosuria.*—Thyroid extract can excite glycosuria. Myxœdema is associated with increased sugar tolerance, while in Graves' disease sugar tolerance is lowered, and there may be actual glycosuria. Hence the myxœdematous patient becomes stout; while the sufferer from exophthalmic goitre emaciates; but even in myxœdema the administration of thyroid extract may cause glycosuria. Garrod found it in four out of eleven cases. The proper dose of thyroid extract in myxœdema is one which does not lower

sugar tolerance appreciably below the normal. The drug is not suitable for the treatment of obesity, unless there is thyroid deficiency, as it may convert a latent into an active glycosuria, for many stout subjects are on the verge of glycosuria.

5. *Pituitary Glycosuria.*—We have already seen that the pituitary body is a factor in controlling carbohydrate metabolism. Recent experiments by J. H. Burn show that this is due to a direct inhibitory action of pituitrin on insulin, preventing it from reducing blood-sugar. In active hyperpituitarism, therefore, there is lowered sugar tolerance, and sometimes glycosuria. In the cases of primary hypopituitarism, known as 'Fröhlich's syndrome,' sugar tolerance may become very high. The development of this exaggerated sugar tolerance may be delayed by compensatory enlargement of the thyroid.

6. *Puncture Glycosuria.*—Recent observations have tended to alter considerably the significance attached to Claude Bernard's classical experiments. It was soon found that puncture of the fourth ventricle excited glycosuria by setting up some nervous irritation, which was believed to act directly on the liver. Then it was noted that previous section of the splanchnic nerve or painting nicotine on the ganglia concerned would prevent the puncture from producing its usual effect. And now it appears that the nervous impulses excited pass, not to the liver direct, but to the adrenals and to the pituitary gland, causing them to throw more of their secretion into the circulation. In short,

puncture glycosuria is adrenal and pituitary glycosuria. The clinical equivalents of this process are seen in the glycosuria of concussion, cerebral tumours, cerebral hæmorrhage, pineal cysts, and the like. But we must remember that now there may be another way in which these conditions may excite a temporary glycosuria, and that is, by pressing on the pituitary body, and squeezing an excess of its secretion into the cerebro-spinal fluid.

I have come across several instances of cerebellar hæmorrhage, which, on account of glycosuria, have been mistaken for diabetic coma. A man walking along the street suddenly felt so faint and giddy that he had to cling to some railings. He was taken to a doctor, who gave him brandy and injected strychnine, whereupon he became unconscious. When he was brought to the hospital comatose, the house-physician passed a catheter and found sugar in the urine. He was treated for diabetic coma by bleeding and infusion of alkalies, but died in a few hours. At the post-mortem examination the urine in the bladder did not contain sugar, and a hæmorrhage was found in one lobe of the cerebellum, which had pressed on the fourth ventricle. I have seen the same thing in a lenticulo-striate hæmorrhage, where the blood had been effused into all the ventricles. In the case here related the sudden onset was unlike that of diabetic coma; but the mistake is very liable to occur in hospital practice when a patient is brought in already comatose, and no clinical history can be obtained. In such circum-

stances the test for diacetic acid becomes of paramount importance, for it will always be found positive in diabetic coma, while it is negative in this type of glycosuria.

7. *Asphyxial Glycosuria.*—In any asphyxial condition glycosuria may occur; this is probably the cause of post-anæsthetic glycosuria, and of the glycosuria of tuberculous meningitis, to which Garrod and Frew have called attention. It appears when the respirations are shallow and grouped. The distribution of the meningitis does not support the idea that the glycosuria results from the pituitary body or the medulla being involved. It is more probably due to the stimulation of the sympathetic nervous system that occurs in asphyxia.

A number of drugs may excite a temporary glycosuria, but they do not throw any further light on its pathology. It is worth while, however, to call attention to the special influence of champagne in this respect, because nervous persons are apt to fortify themselves against the ordeal of life-insurance examination by its aid, with results that are distinctly unpleasing.

The hypothesis of the pancreatic origin of diabetes may be expressed as follows: The stream of sugar entering the portal vein is carried to the liver, but on the way it encounters the internal secretion of the pancreas, which enables the sugar which is not stored directly as glycogen to be utilized by the tissues.

The discovery of insulin may enable us to determine

exactly how this is accomplished. Pavy urged that a comparatively small crystalline molecule, like dextrose, would necessarily escape by the kidney unless it were linked on to a larger molecule, such as protein. The internal secretion of the pancreas may provide links for this purpose. This is supported by Allen's observation that whereas sugar acts as a colloid in the normal individual, it acts as a crystalloid in the diabetic. The linking of the sugar to a larger molecule would cause it to act as a colloid. Another view is that insulin converts ordinary glucose into another form in which it can be rapidly assimilated by the tissues.

Even in a healthy person a sudden rush of ingested sugar may overtax the supply of insulin, and unprepared sugar molecules overflow into the urine. If insulin is somewhat deficient, there will be this overflow after the ingestion of an ordinary carbohydrate meal—alimentary glycosuria. If insulin is gravely deficient, not only will the sugar from the food appear in the urine, but the sugar from the tissues will also pass into the urine. The tissues are now in a condition of sugar starvation, and in starvation the autolytic enzymes come into play. By the breakdown of the cells fresh sugar molecules are set free, not merely from glyco-proteins, but from amine groups like alanin in the true protein molecule. These are equally unable to be used by the tissues which need them, because insulin is missing.

But how can we account for diabetes without

pancreatic disease? We have seen that the glands which control carbohydrate metabolism fall into two antagonistic groups. The first consists of the pancreas, whose internal secretion promotes the utilization of sugar by the tissues, and increases carbohydrate tolerance; the second comprises the thyroid, the pituitary, and the suprarenal, the secretion of each of which mobilizes the sugar into the blood and diminishes carbohydrate tolerance. The second group have two other features in common besides this effect on carbohydrate metabolism: they are all associated with the activity of the reproductive organs, and they all have their secretion controlled by the sympathetic. It is the correlation between this group and the reproductive glands that accounts for the influence of pregnancy in exciting glycosuria.

The main rôle of carbohydrate in metabolism is to provide fuel for muscular energy and to provide for the complete combustion of other foodstuffs, particularly the fats.

The pancreas comes into activity when food is being prepared for absorption into the body; its external secretion is therefore pre-eminently concerned in the storage of energy; the internal secretion acts in the same direction. The pancreas is anabolic, and, like other anabolic activities, is influenced by the vagus, though not to the same extent as some of them. And as the vagus and the sympathetic are opposite in effect when supplied to the same structure, we should expect that the sympathetic would be inhibitory to the

pancreas as it is to other digestive processes. The antagonistic group, like other structures controlled by the sympathetic, come into action when preparation is being made for display of energy.

Sympathetic stimulation is in the primitive state a preliminary to fight or flight. 'Emotion moves us, hence the name,' says Sherrington. Perhaps it would be more correct to say that emotion should lead to movement. But under conditions of civilization the response to emotion tends to be repressed, while preparations for that response still occur. Among these preparations is the mobilization of blood-sugar, which is required for the anticipated display of muscular energy, since active muscle consumes three and a half times as much sugar as resting muscle.

Nervous energy tends to run in accustomed channels. Hence the influence of training. But this equally applies when the nervous energy is perverted; the emotional stimulus may persist because the natural response does not occur and the increased blood-sugar becomes habitual. Allen finds that four days or more of hyperglycæmia are required to produce hydropic degeneration of the cell-islets. Once this is accomplished, the assimilation of sugar will be defective.

It is clear, then, that anything diminishing the secretion of the pancreas or increasing the secretion of its antagonists will lower sugar tolerance and may excite frank glycosuria. Now, when any of the glands controlling carbohydrate metabolism become the seat of organic disease we have seen that there

will be other signs besides the effect on carbohydrate metabolism.

Since improved diagnostic methods of recognizing signs of disease in these glands has not led to their being found in an increasing proportion of cases of clinical diabetes, the polyglandular hypothesis has been put forward to explain diabetes. It was regarded as due to a 'loss of balance between internal secretions.' But how is such a loss of balance brought about? One can understand a loss of balance in a tripod if one leg is broken off. When one gland is diseased the antagonists will show relatively increased activity, just as a group of muscles will show contracture when their antagonists are paralyzed. But when none of the glands are organically diseased, it seems to me that the only way in which a loss of balance can be produced is through a disturbed innervation. And it is clear that sympathetic irritation will at the same time diminish the activity of the gland which promotes sugar utilization, and increase the activity of the group of glands which throw sugar into the blood. And this would soon damage the islands.

It is true that Allen was unable to demonstrate experimentally any effect of emotion in producing diabetes. But it would be difficult to reproduce experimentally in animals the effect of a prolonged depressing emotion on the highly organized nervous system of man. That complete separation of a pancreatic remnant from its nerve-supply does not lower carbohydrate tolerance is beside the mark, for on the

hypothesis here suggested the prevention of inhibitory impulses would not be expected to do so.

Mild cases may become grave if deluged with carbohydrate, while severer cases may acquire a limited tolerance for carbohydrate if properly regulated—that is to say, the types shade off into one another. This suggests some cause which is capable of quantitative alteration, such as a varying amount of internal secretion.

That there is a mild stage without symptoms is proved by the way in which examiners for life insurance find glycosuria in young proposers for policies. There seems a curious liability for a potential glycosuria to become actual under the stress of examination for life insurance, and I have seen several interesting examples of this. Sometimes there has been intermittent glycosuria, which later has become permanent. If it had not been for the insurance examination the glycosuria would remain unsuspected in such cases until the onset of some marked symptom. It points to the conclusion that patients usually suffer from glycosuria for some time before symptoms ensue.

If an examiner for life insurance finds acetone bodies present in the urine without sugar, he should at once suspect that dieting has been practised with the view of enabling a glycosuric to pass muster. A test-meal of 3 ounces of sugar dissolved in water should be given, and the urine tested again an hour later. This is useful also in cases of suspected alimentary glycosuria without the question of attempted fraud.

There would be general agreement, I suppose, in designating the following as examples of mild and severe cases of glycosuria respectively. It would be a mild case if the patient were over forty and not wasting, his tongue not raw, though perhaps covered with a black 'hairy' fur. The urine would contain no acetone bodies. Restriction of the diet would cause sugar to disappear quickly; probably acetone bodies would make a brief and slight appearance now, but so they would in anyone on a suddenly restricted diet. Exercise would cause a diminution of the glycosuria, which shows that sugar could still be utilized by the tissues. A typically severe case would be one in a patient under thirty, who was wasting and had a raw 'beefy' tongue. The knee-jerks might be absent. Diacetic acid would be present in the urine, and sugar still present on a restricted diet. Acetone and diacetic acid would be markedly and persistently increased by a sudden restriction of carbohydrates if proteins and fats were freely taken, and exercise would cause an increase in the glycosuria, indicating that the body was unable to utilize even the sugar set free from the breakdown of its own tissues.

If we had merely to deal with two such distinct classes as these, it would be easy. But, unfortunately for the classifier, all shades of intermediate cases are met with.

Association of Albuminuria with Glycosuria.—There are two conditions in which we may meet with both albuminuria and glycosuria, and the relative impor-

tance of the abnormal constituents of the urine is quite different in each.

(*a*) A patient with granular kidney may have glycosuria, more usually of the amenable type, and sometimes associated with a low blood-sugar. I have seen a striking example of the way in which the glycosuria may mask the more important symptoms of the nephritis. A man who had both albumen and sugar in his urine developed tingling, numbness, and some loss of power in the left side, and became drowsy. His doctor feared that diabetic coma was impending. When, however, I found that there was no diacetic acid in the urine, but that the volume of the urine was diminishing, that the blood-pressure was high, and the aortic second sound was greatly accentuated, I concluded that it was uræmia rather than diabetic coma that was to be feared. Vigorous treatment was directed towards lowering the vascular tension, and the glycosuria was ignored for the time being. Rapid improvement followed.

(*b*) Prolonged glycosuria almost inevitably leads to albuminuria in time. Pavy regards it as the result of irritation of the kidney. As long as it does not cause a rise of blood-pressure, cardiac hypertrophy, or other evidence of arteriosclerosis, one need not trouble very much about the albuminuria. The treatment is merely that of the glycosuria.

The condition of the vascular system and the diacetic reaction will be a better guide than the amount of the sugar compared with the amount of albumen.

The appearance of casts in the urine of a diabetic should, however, always be regarded as serious, and possibly prognostic of coma.

Treatment of Diabetes.

The treatment of diabetes has been enormously improved by alimentary rest and insulin. We now know that diabetes is characterized by a wasteful metabolism. Incidentally sympathetic irritation means increased katabolism and diminished anabolism. Now the quickest method of forcing metabolism to adopt economical lines is to cut off supplies. To realize this, one has only to note the quick fall of nitrogenous output as soon as no food protein is taken. Yet the old method of treatment in diabetes was greatly to increase the amount of protein in the food, thus throwing fuel into the flames. For excess of protein is a great quickener of all metabolic processes. One lesson we all had to learn from the war is that we can balance our metabolism at a much lower level than we previously thought possible. And what was but a passing phase for the normal individual must remain a permanent state for the diabetic. Until insulin was introduced it was necessary for him to be permanently underfed. If he could balance his metabolism when the calorie value of his food was adequate to maintain life and a fair display of energy, the outlook was fairly good; if he could not acquire a balance until the intake was reduced too much for this, the outlook was bad. This was the *rationale* of the fasting treatment of

diabetes. It was not difficult temporarily to rid the urine of sugar, but it might be difficult—nay, impossible—to keep it free when the diet was increased to anything like the level to maintain life. It will be noted that this treatment did not attack the underlying cause of the disease, nor is it yet clear that even insulin does so. Indeed, the disease often progresses, though usually more slowly, during the treatment.

It may be said at once that insulin does not dispense with the necessity for dietetic treatment, and it will therefore be convenient to describe the modern principle of dieting in the first place, subsequently considering the way in which insulin can reinforce this.

The value of intercalated fast-days in the treatment of diabetes has been known for some years. The credit for the initial step must be given to Guelpa, though the premises on which he founded his fasting treatment were incorrect. Von Noorden, in addition to using a modified fasting treatment, introduced days of egg and green vegetable diet. This was originally merely an adjunct to his oatmeal cure, but later observations have shown that the adjunct was more important than the cure itself. Both treatments laboured under the disadvantage that they did not form part of a systematic plan. The building up of the diet on a regular plan, after the fast, was independently arrived at by Allen in America, and by Graham, in London, at St. Bartholomew's Hospital. Unfortunately the war delayed the publication of Graham's results in any comprehensive form. The

principal difference between them is that Allen prescribes a long fast until the urine is free from sugar, and then adds carbohydrate in the form of green vegetable accompanied by very little protein; whereas Graham adopts the plan of a short mitigated fast of 48 hours' duration, followed by a much more speedy addition of protein than in Allen's scheme. My experience is chiefly based on Graham's method, but my general impression is that, whereas Allen's method may get rid of glycosuria more quickly, Graham's is less likely to affect the general health injuriously. The great advantages of their methods are:

(1) Treatment is materially shortened. Formerly one dare not reduce the intake of carbohydrate too rapidly because of the risks of ketosis.

(2) Simultaneously with the reduction of glycosuria there is a reduction in ketosis. Whereas anyone develops ketosis during fasting, in the diabetic this is greatly reduced by fasting, showing that the greater part of it comes from the fat and the fatty acid groups in the excessive protein diet.

(3) The ultimate results were greatly improved. Poulton showed in his Goulstonian Lectures for 1918 that formerly 16·9 per cent. of the cases were fatal during the first year of the disease; by this method only 5·6 per cent. died in the first year. Formerly the average mortality rate was 23 per cent. of all cases admitted—in 1918 it was 7·7 per cent. The ordinary hospital case was comparatively infrequently made sugar-free for even a single day by the older methods,

only 9·8 per cent. being thus freed, as against 73·5 per cent. A patient treated by alimentary rest within three months of the onset had a 75 per cent. chance of being rendered sugar-free indefinitely.

(4) The determination of the sugar tolerance was greatly simplified. Having worked the diet up to a certain level, and the urine remaining free from sugar, it was possible to increase the intake of carbohydrates daily until sugar just returned to the urine. The sugar tolerance could then be easily calculated and the diet drawn up so as to keep definitely below this level.

I will give, in some detail, Graham's plan, which I prefer.

GRAHAM'S METHOD

(Slightly Modified.)

Two Hunger Days.

Tea and coffee, with a little cream or milk, and a pint of Bovril, beef-tea, or clear soup, made without vegetables; divided into two equal portions. Water or lemonade, sweetened with saccharine, can be taken *ad lib.*

The patient should be encouraged to take plenty of fluid.

Two Vegetable and Egg Days.

Breakfast.—Two eggs, scrambled with ¼ ounce of butter. Tea or coffee, with a little cream or milk; 2 ounces of lettuce, watercress, or tomato.

Lunch.—½ pint of Bovril, beef-tea, or clear soup; 1 poached egg on spinach; any vegetables from list below with ¼ ounce of butter. The total amount of vegetables for the meal to be 6 to 8 ounces.

Tea.—Tea or coffee, with a little milk or cream; 2 ounces of lettuce, watercress, tomato, or celery.

Dinner.—½ pint of Bovril, beef-tea, or clear soup; 2 eggs, cooked as desired—*e.g.*, as savoury omelette; 6 to 8 ounces of green vegetables with 1 ounce of butter; water or lemonade as desired.

This diet has a calorie value of 820, and a carbohydrate intake of about 10 grammes.

LIST OF VEGETABLES WHICH MAY BE TAKEN.

Asparagus, broccoli, brussels sprouts, cabbage, cauliflower, celery, cucumber, endive, French beans, lettuce, leeks, radishes, sea-kale, spinach, tomato, vegetable marrow, watercress.

LADDER DIET.

After two vegetable and egg days, add 4 ounces of fish. This raises the calorie value to about 920.

Two days later, add 2 ounces of bacon at breakfast and omit one egg. The calorie value is now 1195.

Two days later, add 2 ounces of sardines at lunch, and omit one egg. The calorie value is now 1335.

Two days later, add 2 ounces of ham, and omit another egg. The calorie value is now 1545.

Two days later, add 4 ounces of meat, divided into two meals, and omit the fish. The calorie value is now 1745.

This diet is generally known as the 'Ladder Diet,' and it will be noticed that it takes twelve days to reach the top of the ladder.

In general terms, I give two consecutive vegetable and egg days once a fortnight, preceded by two hunger days once a month if sugar is present, returning to the standard diet, as determined for the particular patient, immediately after these days. But the details of the after-treatment must depend on the individual case. Rest in bed is advisable, at any rate till the calorie value of the food reaches 1700.

There is one main defect in this method: it is purely conservative. In many instances where it is applied sufficiently early the disease appears to be arrested, but the patient's existence is but a crippled one. Too often, however, the blood-sugar continues to rise, even though a coincident rise in the kidney threshold prevents glycosuria. The hyperglycæmia wears out the cell-islets which means that ultimately the disease must progress.

This is where insulin is such a help; for by keeping the blood-sugar within reasonable limits, it allows of adequate nourishment while the cell-islets have a chance of recovery. That the cell-islets have some power of recuperation, if not overtaxed, Allen's recent experiments prove.

The plan I adopt is as follows: the patient goes through the above course of diet. If he is free from glycosuria at the top of the ladder the blood-sugar is estimated three hours after a meal. If this exceeds 0·18 per cent. he is a suitable case for insulin. Below that figure I continue simply with dietetic measures. If sugar returns to the urine before the top of the ladder is reached, the blood-sugar is estimated, and if, as is almost certain to be the case, there is hyperglycæmia, insulin treatment is begun.

The best plan is to estimate the blood-sugar just before and six hours after the dose of insulin, since this is the length of time the drug continues to exert its effect. I give 10 units hypodermically as the initial dose. From the degree of the drop in the blood-

sugar it can be gauged whether this is appropriate. Where repeated examinations of the blood are not practicable, the following plan serves as a guide: If the urine passed in the three hours before the next dose is due contains a little sugar, there is no risk of overdosage, and the quantity can be increased unit by unit until there is no glycosuria. If this point is not reached when 15 units are given before breakfast or lunch, 5 to 10 units are also given before tea or at 7 p.m., six hours being allowed to elapse between the doses. When the patient has been free from glycosuria for about a fortnight, there are two alternatives, either to increase the food or to diminish the dose. If the calorie value of the food is adequate, and the patient's weight is maintained, the dose can be diminished. If not, the amount of food should be increased while the same dose is maintained. I do not give insulin on the hunger days.

The aim of treatment being to prevent the blood-sugar ever becoming excessive, it is clear that only by repeated estimations can we be certain of this. But with increasing experience fewer tests are needed.

It is true that insulin allows of the assimilation of more carbohydrate. But this does not mean that it is advisable. In one patient of mine a blood-sugar of 0·18 per cent. was raised at once to 0·247 per cent. by exceeding the allowance of porridge, of which he was most anxious not to be entirely deprived. Graham is of opinion that if anything approximating a cure is to be expected, no carbohydrate other than that in

the vegetables should be allowed until the morning blood-sugar has been normal for three or four weeks. There is less objection to this as the risk of ketosis is greatly diminished by insulin treatment, since it leads to the more complete combustion of fat, presumably by promoting the assimilation of the sugar fractions in the protein molecule. Used in this way it is very unlikely that any ill results will follow the use of insulin. It is always advisable to give it just before a meal. The rapid assimilation that follows may excite considerable hunger pain, which presumably means that the blood-sugar is falling rapidly. It is a wise precaution to enjoin rest for six hours after the first dose. The first sign of intolerance is sweating, but subjective discomforts, including some mental confusion, are occasionally complained of. So far I have never had to resort to administration of dextrose, and with carefully controlled dosage this should seldom be necessary. The method of going about with a syringe full of insulin in one hand and a stick of barley sugar in the other carries its own condemnation with it. It will sometimes be found that sufferers from chronic diabetes with a high threshold will not stand a rapid reduction in their blood-sugar. They become uncomfortable at once, and we must proceed gradually. But in cases of impending or actual coma we must act boldly.

Thus in a case under my care, admitted in deep coma, Graham gave 80 units at once, and 110 units in the first twenty-four hours. This case also showed

the influence of focal sepsis in raising blood-sugar, for after a time insulin did not control the hyperglycæmia. Otitis media was discovered and the drum punctured. With the escape of pus the blood-sugar fell again. Although his alveolar air was only 0·9 per cent. on admission he ultimately recovered.

The body normally reacts to sepsis by mobilization of blood-sugar, with the object of exciting pyrexia and thus combating the sepsis. But when the assimilation of carbohydrate is impaired, this merely increases the hyperglycæmia. The observed influence of focal sepsis in lowering carbohydrate tolerance is thus intelligible.

When it is decided that relaxations may be allowed, 100 c.c. of milk (=4 grammes of carbohydrate) should be added, and then, two days later, 10 grammes of bread (=6 grammes of carbohydrate). Increase by the same quantity of bread every other day until the limit of carbohydrate tolerance is reached or the blood-sugar shows a tendency to rise. Then interpolate a day of vegetable and egg diet and return to the former diet with only three-quarters of the amount of carbohydrate on which sugar reappeared.

It will be noted that the modern treatment of diabetes does not really diminish our difficulties with regard to bread. As Osler says: 'Most of the gluten breads are unpalatable, and the rest are frauds.' I distrust all diabetic breads for which, while it is admitted that they are not carbohydrate free, it is claimed that they can be assimilated by the diabetic.

I have frequently found that such claims are unjustified, and the patient, believing that he can take such bread freely, often increases his glycosuria.

Some such breads contain very little less carbohydrate than ordinary bread, and are, of course, much more expensive. On the other hand, a bread which is really free from starch, such as Callard's Casoid (or their Kalari biscuits), is very rich in protein, and on the modern plan of regulating protein intake this offers difficulties. An ounce of their new Casoid bread contains about 9 grammes of protein, and this must be taken into account in constructing the dietary. Allen and Hanbury's diabetic flour, which is caseinogen, may be used in a similar way.

On the whole, it is better to accustom the patient, if possible, to do without bread and get the required bulk of food from green vegetables, and then to allow the small amount of ordinary bread permitted by the carbohydrate tolerance when it has been determined.

In order to afford some variety in the diet I am accustomed to give the patient a table of carbohydrate equivalents, and to state the total amount of carbohydrates permitted.

TABLE OF CARBOHYDRATE EQUIVALENTS.

Thus:		*Gramme. Carbohydrate.*
Bread, 1 ounce	=	16.
Potato, 1 ounce	=	8.
Milk, 5 ounces	=	6.
Green peas, 2 ounces	=	10.
Apples, 2 ounces	=	10.
Artichoke, 2 ounces	=	8.

If, for example, the patient's carbohydrate tolerance has been determined as 50 grammes per day, allowing for the fact that the 'carbohydrate free' diet contains 10 grammes of carbohydrate, the patient is allowed to select not more than 40 grammes from any of the articles in the above table. Sudden relaxations in diet are always dangerous.

The improved treatment of diabetes renders it seldom necessary to give drugs. Codein appears to act by generally slowing metabolism. I only employ it when the plan detailed above has failed to keep the urine free from sugar. Even then I do not give it if there is only a trace of sugar, nor do I give it upon the hunger days or on the days of egg and vegetable diet. The dose starts with ½ grain three times a day, and there is no advantage in increasing it above a grain three times a day. If it does not definitely diminish glycosuria, I do not continue it. It appears to be more effective in the older patients with a mild degree of the disease. I have not been favourably impressed with the effect of pancreatic extracts given by the mouth. The question of giving alkalies is discussed under Ketosis.

If it be objected that I have not succeeded in drawing a sharp line of distinction between the cases of mild glycosuria and severe diabetes, my plea must be that Nature has not done so; it is important to realize that a carbohydrate debauch may precipitate a mild and amenable case into the severe category, while systematic efforts to raise the level of tolerance and

to regulate the blood-sugar may be rewarded by an apparently severe case becoming much milder in type. There is now reason to hope that in this way partial recovery of the cell-islets is possible. With the improved prognosis which alimentary rest and insulin give there is much more encouragement to be patient and persistent in our treatment of diabetes.

CHAPTER X

ACIDÆMIA AND KETOSIS

It has long been known that diacetic acid appears in the urine, and acetone in the breath of a diabetic patient who is progressing unfavourably. But it is now recognized that this symptom appears in many other conditions, such as the recurrent vomiting of children, the pernicious vomiting of pregnancy, broncho-pneumonia, fevers, carcinoma of the digestive organs, rectal feeding, and after anæsthetics.

What general significance is to be attached to a symptom occurring under conditions apparently so diverse?

I. The Significance of Ketosis in Diabetes.

Acetone comes from the decomposition of diacetic acid. The odour, variously compared with that of hay or of apples, is due to diacetic acid rather than to the acetone, which has a more penetrating smell.

It follows that the recognition of diacetic acid in the urine is of greater importance than the detection of acetone, its decomposition product. On the addition of ferric chloride, a claret colour results, which

(unlike the somewhat similar colour seen on addition of this reagent to the urine of patients taking salicylates or carbolic acid), does not appear if the urine has been previously boiled. A more sensitive test for diacetic acid is to add a few drops of a freshly prepared solution of sodium nitro-prusside to the urine, and then pour some strong solution of ammonia on the top. A magenta-coloured ring appears at the line of contact, and diffuses upwards. As shown by Rothera, the addition of crystals of ammonium sulphate makes the reaction still more sensitive. This test was formerly thought to show the presence of acetone till Hurtley proved its real significance.

According to Hurtley the liver converts some of this diacetic acid into the more saturated and less toxic β-oxybutyric acid.* The chemical relationship between these substances is expressed thus:

$CH_3CHOH\ CH_2\ COOH$ = β-oxybutyric acid.
$CH_3CO\ CH_2\ COOH$ = Diacetic acid.
$CH_3CO\ CH_3$ = Acetone.

The terms ketosis and ketonuria are conveniently applied to the presence of these substances in the blood and urine respectively. What is their source?

The sudden and complete withdrawal of carbohydrates from an otherwise liberal diet is known to

* There is no convenient clinical test for this acid. The usual method is, after fermentation to remove the sugar, to distil the concentrated urine with strong sulphuric acid, and to examine the distillate for crystals of α-crotonic acid. β-oxybutyric acid is also lævorotatory.

be dangerous in diabetes. It is followed by nausea, vomiting, loss of weight, the odour of acetone in the breath, the presence of diacetic acid in the urine, and a great increase in the amount of ammonia in the urine. Though the total amount of nitrogen is not altered, the ammonia is greatly increased. Signs of coma may also occur. In one case it is recorded that the ammonia increased from 7 to 29 per cent., and that the blood also became less alkaline. Then the patient was given more carbohydrates, and these symptoms disappeared. A great improvement took place in the general condition of the patient, including the disappearance of the smell of acetone in the breath and the diminution of the ferric chloride reaction of the urine, although there was no marked change in the amount of sugar excreted in the urine.

It is therefore clear that these bodies do not come from carbohydrates, because carbohydrates diminish the amount of them in the urine. Do they come from protein or from fat? Both views have been held, but protein cannot be the main source, for the excretion is not accompanied by a proportionate increase in the excretion of nitrogen and sulphur.

It is possible, however, that some of the fatty acid groups in protein, such as leucin, can give rise to acetone bodies. It has been shown that leucin increased the output of both acetone and β-oxybutyric acid in a diabetic and in a normal man deprived of carbohydrates.

But it is to the fat chiefly we must look as the source of the acetone bodies.

Geelmuyden and others produced ketosis in healthy persons by a fatty diet. In one case the sole diet daily for five days was 250 grammes of butter, 200 grammes of oil, and a little wine. β-oxybutyric acid, diacetic acid, and acetone were then as abundant in the urine as in the severest cases of diabetes, while 37 per cent. of the total nitrogen was in the form of ammonia.

The Element of Starvation.—Anyone can produce ketosis by starving himself. In some diseases associated with ketosis the element of starvation is obvious—for instance, in carcinoma of the digestive organs, certain febrile conditions, and rectal feeding. A wasting diabetic is being starved also from inability to metabolize carbohydrate.

Of all the tissues, the fat loses most in starvation, the more noble organs being fed at the expense of the less essential ones. To effect this, the fat must be broken down, in the course of which fatty acids would be set free. If fat has been got rid of previously, acetonuria is not so marked a feature of starvation, while a fatty diet accentuates it.

An easily assimilable food, such as dextrose, leads to a prompt diminution or disappearance of the acetone bodies. That the acetonuria of febrile conditions could be largely inhibited by supplying the wasting tissues with carbohydrates von Noorden proved as follows: In two cases of typhoid fever, he gave patient A a diet with very little carbohydrate in it, and patient B one with plenty of carbohydrate. A had a marked

diacetic reaction, and B only a trace of acetone. After a few days the diet was reversed, with the result that the former showed only a trace of acetone, and the latter a well-marked diacetic reaction. Meyer has made similar observations on children suffering from various acute infectious fevers. Halpern has recorded the case of a man with an œsophageal stricture, whose only food for twenty-six days was 30 grammes of grape sugar *per rectum*, yet his urine contained no acetone or diacetic acid. The quantity of carbohydrate sufficient to abolish the acetone bodies from the urine does not supply so much energy as was being provided by the fats, so that the carbohydrate does not merely act as a fat-sparer.

Von Noorden attributes the rôle of carbohydrates in preventing ketosis to their relative abundance in oxygen, which is drawn upon to complete the breakdown of the tissues into CO_2 and water. In their absence the less completely oxidized fatty acids appear. Zeller showed that it was necessary for one molecule of carbohydrate to be metabolized to lead to the consumption of two molecules of fat without ketosis.

In Rosenfeld's phrase, fats are consumed in the fire of the carbohydrates. Ketosis has been called the smoke from the fires of metabolism.

Other substances besides carbohydrates, however, such as alcohol, tartaric, citric, and glutaric acids, all seem capable of diminishing the output of the acetone bodies to a limited extent. The benefit of citrates in diabetic ketosis has been explained as due to their

neutralizing the abnormal acids by becoming bicarbonates in the blood. But apparently this is not the only way in which they act.

To summarize—the ketosis of diabetes is due to the abnormal breakdown of fats necessitated by non-utilization of carbohydrates.

II. On Acidosis in General.

To appreciate the significance of ketosis and acidæmia in general, it is necessary to consider the equilibrium between acids and bases in the blood. The subject is still controversial, and only such aspects of it as have a direct clinical bearing will be touched on.

Acidæmia has been defined by Barcroft as an increase of acid relative to basic radicles in the blood, CO_2 not being considered. It may be produced, therefore, either by excess of various acids, such as diacetic and lactic, or by defect of alkaline salts. It may be *physiological*—thus if there be a lack of oxygen, lactic acid is produced, which, like other acids, stimulates the respiratory centre to increased exertion, with resulting more vigorous ventilation of the lungs. This is seen in the acidæmia which occurs when exercise is taken, whereby increased oxygen intake is provided. Physiological acidæmia also occurs at high altitudes, when, although the body is at rest, there is anoxæmia from the lowered pressure of oxygen in the atmosphere. Hasselbalch showed that in this case the urine became more alkaline, and the formation of ammonia

from tissue proteins was diminished. He attributed this to an adaptive mechanism on the part of the kidney, which, by excretion of alkali, increased the fixed acids in the blood. Haldane and others have shown, however, that it is more probable that anoxæmia caused an over-ventilation of the lungs which led to excessive elimination of CO_2. Hence the blood would tend to become more alkaline, unless this was rectified by less ammonia formation and a more alkaline urine. On this view anoxæmia tends to upset the balance in the direction of alkalæmia rather than of acidæmia, which has to be compensated for. This may also occur in the dyspnœa of heart disease, where the stimulus to the respiratory centre would appear to be the oxygen want resulting from capillary stasis.

When acidæmia results from some pathological condition which actually increases the production of acid, it may be compensated or uncompensated. It can be *compensated* for by (1) increased ventilation of the lungs, which diminishes the amount of CO_2 in the blood; (2) increased excretion of acid phosphates; (3) increased formation of ammonia from the tissue proteins. Therefore, pathological acidæmia can be recognized by the increased excretion both of acid and of ammonia, while in physiological acidæmia both would be diminished in the urine.

If the acidæmia is *uncompensated*, toxic symptoms may result, simply from excess of acid radicles in the blood. If an animal were intravenously injected with a sufficient amount of dilute solution of hydrochloric

acid it would be possible to render its blood actually acid, and death might be due to this alone; this would rightly be called 'acid' intoxication. But if, for instance, dilute hydrocyanic acid were used, death would occur before any perceptible alteration in the reaction of the blood had occurred, owing to the specific poisonous character of the acid. Which of these two factors is responsible for diabetic coma?

The similarity between the poisoning of dogs by injection of acids and the phenomena of diabetic coma is very great. In both there is greatly increased respiration, rapid pulse, increased ammonia excretion, and diminished CO_2 in the blood. But whereas in dogs the condition can be rapidly improved by administering alkalies, this treatment is most disappointing in diabetic coma. Pavy held that the acidity of the blood in diabetic coma reduced its capacity for carrying CO_2 which, accumulating in the tissues, caused narcosis. But in that case the increased CO_2 tension in the renal cells, for instance, would be communicated to the urine, and this does not occur. Poulton determined the hydrogen-ion concentration of the blood to be normal in seven diabetic patients who were definitely drowsy. These facts show that, though abnormal acids are present in diabetic coma, mere acidity is not responsible, and the acidæmia is indeed often compensated. We are thrown back on the other explanation that the coma is due to the specific poisonous action of some acid.

Yet another condition is possible: acidæmia may be *over-compensated.* Certain substances containing the group COH=CH were shown by Hurtley and Trevan to have a stimulating action on the respiratory centre, quite apart from any acid reaction they may possess. This would cause hyperpnœa, with consequent washing out of CO_2 from the blood, so that its alkalinity might in fact be increased. This has actually been observed by Van Slyke. Diacetic acid contains this group, and sodium diacetate may produce a hyperpnœa out of all proportion to the amount of acid present. Hurtley, therefore, refers diabetic coma to the poisonous effect of diacetic acid, and not to its acidity.

It must be confessed that non-diabetic ketosis is very seldom really toxic in its effect, though, of course, toxic symptoms may coexist with it. In some cases ketosis is evidently secondary to starvation, as already stated. Œsophageal or gastric carcinoma, cyclical vomiting in children, and pernicious vomiting in pregnancy are examples of this. In eclampsia and post-anæsthetic poisoning there are severe toxic symptoms probably due to interference with the oxidases of the liver, but the ketosis is only one and probably not the most important manifestation of this. In uræmia there is an acidosis which is at first compensated, but which becomes uncompensated, when the dyspnœa at rest becomes at all marked. Lewis and Barcroft showed that it was associated with the presence of some non-volatile acid. I should agree with Marriott and Howland that it is due to the failure

of the kidney to excrete acid phosphates. In cardio-renal cases the factors of this excretory failure and of oxygen want will both be operative.

III. Symptoms Associated with Acidæmia and Ketosis Intoxication.

(*a*) *In Diabetes.*—The cardinal symptoms have already been dealt with, when considering the effect on a diabetic of sudden deprivation of carbohydrates. But milder manifestations of this sort are not infrequent in the more amenable type of diabetes. If 'bilious attacks,' accompanied by some drowsiness, occur, they will usually be found to be associated with the appearance of acetone and diacetic acid in the urine, though these bodies may have been previously absent.

The ordinary symptoms of diabetic coma are too well known to need restatement. What is not so generally known is that the over-compensation resulting from the stimulation of the respiratory centre causes a drop in the CO_2 of the alveolar air to a point below the normal 5 per cent. Analysis of the alveolar air may lead therefore to a recognition of the impending danger, before air hunger is obvious. I should like to call attention to the influence of excitement, fatigue, constipation, and carbuncles in inducing coma in the diabetic, and to the frequency of severe pain in the throat or epigastrium just before it occurs. Poulton lays stress on the effect of diacetic poisoning on the

circulation, as shown in the weak pulse and empty condition of the veins.

(*b*) *In Recurrent Vomiting.*—In 1882, Gee described cases of fitful and recurrent vomiting of unknown causation in children. Later observers noted acetone in the breath, urine, and vomit. Diacetic acid and oxybutyric acid have also been found when looked for. The analysis of fifty-five cases by Batty Shaw and Tribe gives the following clinical features: The cases usually occur between three and eleven years of age. The frequency of the attacks is very variable, a common interval being three months. There may be a prodromal period, in which dyspnœa, sighing respirations, offensive breath, choreic movements, and general restlessness have been noted. The tongue may either be coated or clean. Then vomiting begins, without nausea, and usually without gastric pain, all food is rejected, and towards the end of the attack bile appears, sometimes even blood. Constipation is common. The attacks may last only a few hours, but the average duration is five or six days. It is the rule for fever to occur during the attacks of vomiting. Wasting is often a very marked symptom. In later life these attacks are sometimes replaced by migraine, but they tend to disappear when puberty is reached. Three of the fifty-five cases were fatal. A mild degree of such a condition is, I believe, quite common in children, and I would venture to suggest that 'biliousness,' which, as Gee said, is a real state, a very common state, but a state that is little understood, is also of this character.

In some cases the appendix is responsible; in others there may be bacilluria. Probably the liver is put out of work by some toxin, and in many cases this toxin may be due to the *B. coli* which has invaded the biliary passages, or to the *B. aminophilus*, which can form poisons from histidine. This would explain why the prompt use of a mercurial purge may ward off an attack. When once the liver fails to do its work, the tissues are starved, and, in their autolysis, produce these abnormal acids. The vomiting accentuates the condition by increasing the starvation and the loss of saline bases.

(*c*) *In the Pernicious Vomiting of Pregnancy.*—Though the pernicious vomiting of pregnancy may be due in some cases to mechanical causes, such as displacement of the uterus, the majority are due to neurotic causes. There probably remains, however, a more serious group in which a toxæmia is responsible. In these toxæmic cases, necrosis and degeneration of the central portion of the liver lobule, and necrosis of the excretory portions of the kidney, have been found by Whitridge Williams. He found also a striking increase in the percentage of nitrogen eliminated as ammonia, which, compared with the total nitrogen of the urine, amounted to 16, 32, or even 46 per cent., instead of the normal 3 to 5 per cent. He suggested that this might be due either to failure of urea formation in the liver, or to the attempt to neutralize acid intoxication.

Dr. Helen Baldwin found, in such a case, that the urine yielded a marked reaction for acetone and diacetic acid, but no sugar. The patient's condition

was so serious that labour was induced. After this the abnormal acids diminished, until only acetone was found. On the tenth day after the induction of labour there was a return of severe headache, nausea, and vomiting, and it was noteworthy that, on this day, diacetic acid was again found in the urine. After this recovery was uninterrupted.

But Williams' interpretation of these facts is open to several objections. A very small proportion of the liver substance is sufficient to carry out the conversion of ammonia into urea. Extensive necroses have been produced experimentally in the liver without raising the percentage of ammonia.

In starvation from any cause the percentage of ammonia increases, mainly because of diminished urea excretion, which must occur since so much of the urea is derived directly from the nitrogenous food. Thus, the total nitrogen output in Williams' cases was lower than that found by Cathcart in his fasting man and that which I have found in cases of hæmatemesis receiving saline enemata only. Now the absolute amount of ammonia nitrogen in Williams' first case during the vomiting was 1·44 grammes, while a month after labour had been induced it was 1·21 grammes. These differences are not so great as those observed by Cathcart in a professional faster, in whom the ammonia nitrogen was 0·6 gramme before and 1·4 grammes during the fast.

When ammonia is expressed in percentages, these important facts are obscured, and an ammonia co-

efficient reaching to 32 or 46 per cent. is apt to acquire an undeserved significance.

Leathes puts it very fairly when he says: 'Before it can be safely maintained that these high figures are a sign in themselves of a toxæmia that is likely to prove fatal unless the most active measures be taken, it is necessary to prove that they are not sufficiently accounted for by some of the attendant circumstances of the patient's condition—the low nitrogen content of the absorbed food, the imperfect nutrition due to the incessant vomiting, the loss of alkali in the vomit, aggravated possibly by the requirements of the fœtus.' In other words, the high ammonia coefficient may result from simple starvation, rather than from an attempt to neutralize acids. Some cases recently reported by Gilliatt and Kennaway (*Quarterly Journal of Medicine*, 1919, vol. xii., p. 60) appear to fulfil Leathes' requirements, for here the ammonia index showed a rapid increase which could not be accounted for by starvation. But Hurst's observations tend to support the view that most cases of pernicious vomiting are nervous in character.

(*d*) *In Gastro-Intestinal Ketosis.*—Here the ketosis merely results from starvation, and is not in itself responsible for symptoms, though it is naturally associable with rapid wasting.

(*e*) *In Broncho-Pneumonia.*—Garrod associates drowsiness, torpor, and vomiting with the presence of diacetic acid in the urine.

The principal symptoms, then, which seem to be

commonly associated with the various forms of ketosis are dyspnœa, wasting, vomiting, drowsiness, and coma.

Post-Anæsthetic Ketosis.—That death might follow the delayed action of chloroform was first suggested, so long ago as 1850, by Casper. In this country, Leonard Guthrie drew attention to the condition in 1893, and much interest and discussion has been aroused. Other anæsthetics besides chloroform were also found to cause it.

Twelve hours or so after the anæsthetic the patient (usually a child) suffers from profuse and repeated vomiting, the vomiting eventually resembling the dregs of beef-tea. Sometimes there is a preliminary period of restless excitement and delirium.

This is followed by drowsiness, apathy, and unconsciousness, deepening to coma. Death usually occurs about the fifth day, but sometimes later, from gradual or sudden cardiac or respiratory failure. Pyrexia is not the rule, though the temperature may be very high just before death. The pulse becomes very rapid. Albuminuria with casts is common. Furthermore, there is a smell of acetone in the breath, while diacetic acid is found in the urine. It will be noted that these symptoms resemble in essentials the features of other ketoses; but the abnormal acid was only looked for at first where something went wrong after anæsthetics.

It is now generally agreed that diacetic acid is often present in the urine after anæsthetics, and not uncommonly before. Frew has shown that in children

the mere change of diet accompanying admission to hospital is sufficient to induce ketosis. As the hospital diet is rich in carbohydrates, it is not due to starvation but to the fact that the child apparently takes three days to adapt its digestion to the change. Now the majority of children that are admitted for operation receive their first anæsthetic within three days of admission—that is to say, while ketosis is already present. In addition to this, tradition demands that the patient should be starved both before and after operation, and that an acute diarrhœa should be induced. In short, everything is done to induce ketosis, and then a toxic vapour is given, and an operation is performed which further lowers vitality. It is curious that toxic symptoms do not occur more frequently. Possibly the concentration of the anæsthetic vapour has something to do with it, a high percentage having a more injurious effect on the protoplasm of the liver than a low one.

The most striking change noted post mortem is fatty degeneration of the middle zone of the lobules of the liver, with necrosis of the central part. To the naked eye the liver appears large and canary-yellow in colour. This change can occur very rapidly. Thus Telford saw a liver to be normal while performing a gastro-enterostomy; toxic symptoms followed, and at the post-mortem the liver was slightly enlarged, bright yellow, and loaded with fat. This is a point against Guthrie's view that the anæsthetic is merely the last straw, acting on a previously fatty liver, to which feed-

ing up with fat may have contributed. The anæsthetic has been the last straw indeed, but by increasing a previous ketosis to the point of a toxic acidæmia.

All anæsthetics are solvents of fat, and the breaking down of such dissolved fats could give rise to excess of fatty acids. But many very fat people have been exposed to long administration of chloroform without these after-effects.

Why should fat in the liver behave so differently to fat in other parts?

In the chapter on the work of the liver it was shown that this organ prepares fat for the use of the tissues by desaturating it. If it is unable to do this the fat from other organs which is sent to the liver to be thus prepared merely accumulates there. The conclusion to which we are led is that, while anæsthetics and the preparation for them may cause ketosis, they will not cause toxic symptoms unless the liver is thrown out of gear at the same time, perhaps by inhibition of the oxidases. A diseased liver will naturally be more easily affected than a sound one. Deprivation of readily assimilable carbohydrate is the most effective way of inducing the catastrophe of post-anæsthetic poisoning.

IV. Treatment of Acidæmia and Ketosis.

The indications for treatment are—

1. To prevent further formation of fatty acids as far as possible. Broadly speaking, this will be accomplished by promoting the assimilation of carbohydrates.

2. To neutralize the acids already formed, and supply the deficient bases.

By what methods can these indications be put into effect?

(a) *In diabetes* the fasting method has given us a plan for simultaneously attacking the glycosuria and ketosis. As already pointed out, whereas fasting produces ketosis in the normal individual, it greatly diminishes it in the diabetic already suffering from it. In other words, the drop in toxic ketosis far outweighs the rise in fasting ketosis.

Von Noorden some years ago noted that a diabetic *previously free from* acetone would show some acetonuria at the beginning of a restricted diet. He urged that this did not indicate an immediate relaxation of diet, and that if such relaxations were made the advantage of the dieting would be lost. This empirical observation was not understood at the time, but now receives its explanation in the difference between fasting and toxic ketosis. The former may be neglected, the latter always calls for treatment. The fact that acetonuria is present, therefore, does not contra-indicate a fast, though some observers are of opinion that a few days of a diet, in which the amount of protein is considerably reduced and fat is hardly taken at all, is a useful preparation for the fast in chronic or debilitated cases. I have, however, come to the conclusion that marked ketosis only increases the need for prompt alimentary rest.

The most effective method of attacking ketosis is,

of course, to raise the carbohydrate tolerance. This, too, is best effected by alimentary rest and insulin, as explained in the chapter on diabetes. As the incapacity to metabolize carbohydrate is rarely complete, attempts have been made to find some form of carbohydrate which could be more readily assimilated than others—hence the 'Oatmeal Cure' and 'Potato Cure.' To-day we realize that it is quantitative rather than qualitative regulation that is called for. An exception may be made in the instance of levulose, which does not raise the sugar in the blood. The capacity of a diabetic for lævulose is, however, limited to the amount which his tissues can consume on the spot. This will not exceed 20 grammes (5 drachms), divided into several doses in the day. If more than this is given, it is stored as glycogen, and subsequently converted into dextrose. Its cost, however, is prohibitive except for wealthy patients, or in emergencies such as threatened coma. Artichokes are rich in insulin, which breaks down into lævulose. This is a cheaper method of supplying it, which sometimes helps. But the introduction of insulin makes the use of lævulose unnecessary.

While *bearing in mind the dangers of the alcohol habit, it nevertheless may be sometimes advisable to give alcohol to the extent of about an ounce of the pure spirit in the day, because of its being able to replace* carbohydrates to a limited extent in metabolism. Malt liquors, sweet wines, champagne, and liqueurs will naturally be avoided.

With the treatment already advised for diabetes the administration of alkalies is much less necessary than formerly. Indeed, some observers, such as Joslin, maintain that they are actually harmful, though I do not think there is positive evidence of this. Their usefulness is certainly limited by the facts that diabetic acidosis is often over-compensated, and that diacetic acid seems to be toxic in itself and not merely because it may increase the acid ions in the blood. At the same time they can save the loss of nitrogen in the form of ammonia, which is obtained from protein and excreted in combination with the diacetic acid.

Spriggs has shown that if 2 drachms of sodium bicarbonate be given to a normal individual, the urine becomes alkaline and remains so for twenty-four hours. But if excess of acid is being formed, this amount is insufficient, and the amount of bicarbonate that can be taken without producing neutrality or alkalinity of the urine may be regarded to some extent as a rough measure of the degree of acid production. A more accurate measure is the amount of ammonia in the urine, which can be quickly estimated by the formalin method. In severe cases it may be impossible to make the urine alkaline.

I usually give citrate of potash as well as bicarbonate of soda, because it is not neutralized by the gastric juice, and becomes bicarbonate in the blood, where the alkali is most needed. It seems particularly suitable in those milder cases of diabetic acetonuria in which some drowsiness and 'bilious' symptoms are present.

But the advantage of citrates does not end here, since citric acid appears to diminish the production of acetone bodies.

It is not sufficient to supply the body with bicarbonate of soda, as is generally done; other bases should be given also, especially as in diabetes there is a drain on the calcium and magnesium. To give sodium salts alone disturbs the balance of salts in the body.

A mixture such as this—

Sodii bicarb.	ʒi.
Pot. citrar.	gr. xxx.
Calcii carbonatis	gr. iii.
Magnesii carbonatis	gr. iii.
Aquam	ad ℥i.

is of more service, because *the amount of K_2O excreted* daily is one-half that of the Na_2O, while the CaO and MgO are each one-twentieth of the amount of the soda. Half to one ounce of this mixture may be given three times a day, or every four hours when indicated.

Much may be done towards preventing coma by careful attention to the ketosis. A rise in the ammonia *output to 4 grammes* a *day is very ominous.* As soon as coma *threatens, 20 to 30 units of insulin* should be *given, the rectum cleared out by enema,* and 5 per cent. *of sodium bicarbonate run slowly into the bowel until about 1½ litres of fluid have been* administered.

Intravenous infusion with bicarbonate of soda is seldom practised now. Owing to the empty con-

dition of the veins in coma no attempt should be made to put a needle into one without cutting down on to it. But the discovery of insulin has given us a far more potent weapon. Before this, once coma had developed, the duration of life was to be measured by hours rather than days. It was realized that the proper treatment was prophylactic, since coma is often the result of improper dieting with excess of protein and fat. Even with insulin the condition is a dangerous one, but not hopeless. The amount of insulin which can be given in coma without serious consequences is astonishing. In the case I have already referred to, 110 units were given in the first twenty-four hours, and for ten days after this the daily dose varied from 70 to 90 units, no individual dose exceeding 30 units. On one day when coma threatened to reassert itself, as much as 140 units were given.

(*b*) *In the Recurrent Vomiting of Children.*—To ward off attacks, prodromal signs should be noted—white stools, offensive breath, some change in complexion, usually indicative of what are called 'bilious attacks,' and the presence of abnormal acids in the urine—then mild aperients and easily digestible foods are indicated. Barley-water is usually tolerated. Small doses of grey powder or calomel should be given, also bicarbonate of soda, up to 3 drachms in the day. Normal salt solution *per rectum* is useful. I would suggest that arrowroot might be employed, on the principle that the abnormal acids are checked

in their production by the administration of carbohydrates. Certainly 4 per cent. of dextrose added to the rectal saline will often help. Bacilluria should be treated if present, and if an X-ray examination indicts the appendix it should be removed.

(c) *In the Pernicious Vomiting of Pregnancy.*—Whitridge Williams recommends that when the amount of nitrogen in the form of ammonia rises from the normal 3 or 5 to 10 per cent. of the total, labour should be induced. We have already seen, however, that this ammonia coefficient may be a fallacious guide. A sudden rise to a higher level such as 30 to 50 is a surer indication of the necessity of such a drastic procedure. In the nervous type remarkable results may be obtained by encouragement by suggestion. It may be helpful to give bromide, and, if necessary, *per rectum.* Some observations by Longridge on eclampsia show that the same general line of treatment as in other forms of ketosis may be helpful, although this condition differs from pernicious vomiting. He noticed a diminution of alkalinity of the blood and gave citrates with the object of bringing up the diminished alkalinity of the blood to normal. Sugar was also given by the mouth and rectum.

(d) *In Post-Anæsthetic Poisoning.*—(1) Before operation on even fat and apparently healthy children careful inquiry should be made as to the history of so-called 'bilious attacks,' which may in reality be those of ketosis (Guthrie). (2) Where possible, operation on a child should be delayed until it has been

accustomed to the altered diet in hospital. The urine should be examined for diacetic acid, and, if present, alkalies should be prescribed. (3) Both starvation and fright cause acidosis. Four hours' fast for children before operation is too long. Saline enemata containing 2 to 5 per cent. of dextrose should be given after the lower bowel has been cleared, two hours before and immediately after operation. The effect of fright cannot be altogether controlled, but may be diminished by preventing starvation. Should symptoms of ketosis occur despite these precautions, it must be treated as in other cases. Dextrose must be got into the system somehow, and Beddard recommends that if it cannot be retained in the stomach, it should be given by continuous rectal infusion of a 10 to 20 per cent. solution, or even by infusing intravenously a 6 per cent. solution. I should prefer 5 per cent. for rectal irrigation as less likely to irritate the bowel. Once post-anæsthetic vomiting is established, bicarbonate of soda and other alkalies must be given freely to neutralize the acids already formed.

Insulin has been recommended for the treatment of non-diabetic ketosis, but it is too soon to express an opinion on this. In the only case in which I have seen it tried I was not favourably impressed with the effect.

CHAPTER XI

INTESTINAL INTOXICATIONS

THERE are fashions in pathology, as in dress, and intestinal intoxications have come in for a large share of attention in recent years. Most diseases of hitherto unexplained causation are now referred to this. It is such a fatally easy explanation that it is but human to yield to the temptation in face of perplexity.

Englebert Taylor well says that 'the progress of the auto-intoxication theory, like that of every other uncontrolled movement in practical medicine, is like the development of gossip in common life: the first person suggests that it might be so, the second states that it is so.'

Yet the subject is one of very practical importance. The alimentary canal is an open door for infection, and it is quite probable that many cases of chronic and indefinite invalidism depend upon intoxication by this route. Therefore, it is worth while to consider what is really meant by an intestinal intoxication, and what symptoms it might be expected to cause. We can then examine the evidence necessary to establish the

fact that intoxication has occurred, and inquire how far that fact is proven in some special cases. Progress cannot be made by haphazard references to pyorrhœa and constipation, important factors though they be. The mechanical factors in inducing toxæmia by intestinal stasis have already been discussed in Chapter III. Here we are concerned with the chemical factors.

'The mucous membrane of the alimentary canal is pre-eminently an absorbent surface—it is constantly bathed in liquids swarming with bacteria.' The flora is both varied and extensive, yet how seldom can infection by pathogenic organisms or intoxication by saprophytes be proved.

Probably microbes constantly invade the body from the alimentary canal, but are as constantly destroyed. Flexner has shown how frequently a terminal infection occurs when the vital forces of the body are exhausted. Metchnikoff compares the leucocytosis of digestion to the leucocytosis in certain infections, believing them to be due to the same cause—the resistance of the body to invasion. The comparison is at any rate suggestive. The body possesses four lines of defence against intestinal intoxications and infections: Firstly, the epithelial resistance; secondly, the bactericidal properties of the blood; thirdly, the antitoxic functions of the liver; fourthly, the internal secretion of the thyroid, and possibly of other ductless glands.

Gastro-intestinal intoxication may result from—

1. Inorganic poisons—*e.g.*, lead, arsenic.
2. Organic poisons—*e.g.*, cyanides, foreign proteins.

3. Intermediate products of digestion—*e.g.*, peptones, purins.

4. Products of putrefaction—*e.g.*, indol.

5. Products of abnormal pathogenic bacteria present in the intestine.

The first two do not concern us here. The reaction of the body against them differs in important respects from the method adopted against bacterial poisons. The neutralizing substances are normally present in the body, and are not specific, each of them combining with several poisons. Fromm points out that these reactions are few and simple, such as oxidation, reduction, hydration, dehydration, and methylation. The protective substances also are few, such as proteins, bile acids, glycuronic acid, etc. They are not the result of any special adaptation to meet a pathological condition. They are there as the result of normal metabolism; they have an affinity for various chemical substances, some of which happen to be poisons. If these enter the body, they are neutralized to some extent, though, as a rule, very incompletely. This is a very different reaction from the formation of highly specific immune substances against bacteria and their products.

Intoxication by Intermediate Products of Digestion.

Peptone is not the end-product of digestion, but the process is carried further to simpler amine bodies. As intravenous injections of proteoses and peptones will cause symptoms, it has been suggested that intestinal intoxications may result from absorption of these intermediate products, the toxic effect decreasing with the decreased size of the molecule. But there is no definite evidence that such an absorption occurs.

Passing from the simple to the compound proteins, nucleo-proteins are credited with a toxic power on account of the purin bodies that they contain; but, normally, the liver largely destroys these.

The importance of the detoxicating action of the liver has already been referred to. Even in normal digestion the absorbed products are not sufficiently elaborated to be used by the tissues. A further step has to be taken by the liver, and this is one of the most important metabolic functions of that organ. When in a disease we find an intermediate product of normal metabolism excreted in the urine, I think we must conclude that hepatic insufficiency rather than intestinal intoxication is the cause of the toxic effects observed.

Intoxication by Products of Putrefaction.

Whether digestion can be carried on aseptically is a purely academic question, since the opportunity never arises. The infant starts with a sterile alimentary canal, but speedily acquires bacteria therein, chiefly organisms derived from the skin of the mother's nipple. In the intestine of bottle-fed children there are many more organisms of the *Bacillus coli* class. The *Bacillus putrificus* begins to appear in childhood, and the flora of the intestine becomes large and varied.

Now, in putrefaction abnormal products of disintegration may be set free, and we must inquire into their responsibility for symptoms. The great seat of putrefactive change is the large intestine. Proteins putrefy, carbohydrates ferment, and to a certain extent these two processes are antagonistic. Fermentation may be useful to animals that eat a large quantity of uncooked vegetables, because the cellulose resists the ordinary digestive juices, so that until the cell-walls are dissolved by bacterial agency the contained foodstuffs are not available. This, however, is not much use in human beings; but fermentation plays another useful part in antagonizing putrefaction, which might lead to the development of more toxic substances. Putrefaction is the disadvantage of a large intestine, the advantage being that, by the absorption of water there, the bulk of the fæces is greatly reduced, so that the emptying of the bowel need not occur normally more than once a day. There is also less need for

drinking large amounts of fluids. According to Metchnikoff, the disadvantages outweigh the advantages, and, in fact, he looks upon old age as the result of chronic intoxication from the large bowel. That animals with a short colon are long-lived is, in effect, his conclusion; and it seems to be the opinion of some surgeons that it is better for a man to dispense with the services of his colon than to possess an indolent one. Yet we can hardly suppose that the colon would have appeared in evolution without the development of a compensatory protective mechanism. And we have evidence of its existence. Indeed, the proof of intoxication by the products of the ordinary putrefactive changes in the intestine is quite inconclusive. Let us see what these changes are, and how far any of the resultant bodies can be incriminated.

Proteins undergo the most changes in putrefaction. Whatever the protein, it contains the same four groups, however different the representatives of those groups may be.

Mon-amino Fatty acids—*e.g.*, Leucin.	Hexone Bases—*e.g.*, Arginine.	Aromatic Bodies—*e.g.*, Tyrosin. Tryptophan.	Cystin containing S. SO_2

Putrefaction would seem mainly to affect the right-hand groups in this diagrammatic scheme—*i.e.*, the aromatic bodies and the sulphur groups. Tyrosin yields phenol compounds, while tryptophan yields

indol and skatol; the oxidized sulphur appears as sulphates, and the unoxidized as cystin.

The sulphates conjugate with the aromatic bodies in the liver to form ethereal sulphates which are practically harmless. These ethereal sulphates appear in the urine. Indican is one of them, being indoxylsulphate of potash. As this is readily detected in the urine by its striking colour reaction, much of the theory of intoxication by putrefaction centres around it.

The tests usually employed are—

1. To 2 inches of urine in a test-tube add an equal quantity of strong HCl and 3 drops of hydrogen peroxide (10 volumes per cent.); add ½ inch of $CHCl_3$, and shake up thoroughly. If indican be present, the $CHCl_3$, when it has again sunk to the bottom, will be tinged blue. This is a very sensitive test.

2. A little ferric chloride may be used similarly with the strong HCl (Obermayer's test). It is best to precipitate phosphates first with lead acetate.

But we cannot conclude, simply from getting this striking reaction, that we are dealing with a case of intestinal intoxication. The ethereal sulphates are not themselves toxic, and even if they were, we cannot judge of their total amount by indicanuria alone, which only represents one of them. The amount of reabsorption will be also influenced by the rate at which the contents are passing along the canal.

There is normally very little indican and other ethereal sulphates in the urine of children and adolescents, but putrefactive processes are more abundant

in middle life. Indicanuria is common in students leading sedentary lives. Herter found that the body has the power of rapidly transforming considerable amounts of indol, since, even after injecting as much as ½ gramme into the femoral vein of a dog, he was unable to detect any in its blood.

Repeated administration of indol to rabbits causes loss of weight, among other symptoms. In man, taking considerable amounts causes headache, with indisposition for mental or physical exertion. The muscles respond as if fatigued. Herter suggested that if prolonged, this may lead to neurasthenia. In thirty-two cases of neurasthenia he obtained a marked reaction for indican twenty-one times, a slight or no reaction eleven times. He concluded that while indol is not a highly toxic substance, people with a persistently strong indican reaction invariably suffer from nervous or dyspeptic disorders, and that many with well-marked indicanuria have to live carefully to keep fit. He regarded those with soft arteries, little indican, or ethereal sulphates as 'candidates for old age.' Exceptionally there may be enough indican in the urine to form a blue pellicle on the surface without addition of reagents. The subjects of this condition are almost invariably badly nourished and in poor, almost precarious, health. But it is not desirable to single out indicanuria as the sole object of treatment, as it is linked to other intestinal conditions.

I would suggest that, whether such substances do or do not exert their toxic effect depends largely on

whether they are free, or whether there is sufficient sulphate for them to combine with, in which state they are harmless. In support of this, I may refer to a striking case described by Garrod. He examined the urine of a lady who for many years had applied a carbolic dressing to an ulcer on the leg. He reported that she was on the verge of carboluria. Her medical man proceeded to put this statement to the test by giving her 20 minims of carbolic acid internally. He had the satisfaction, at any rate, of knowing that he had obtained a correct opinion, for his patient promptly had a smart attack of carboluria! Garrod's opinion was based on the observation that almost all the sulphates were in the form of ethereal sulphates—*i.e.*, her power of neutralizing the toxic effects of phenol was taxed almost to the full. A little more and she was over the brink. Now, indol is closely related to phenol chemically. This points to two considerations: (1) When we test for indican, we are testing for just that part of the indol which has been rendered inert. (2) We may here have an explanation of the comparative failure of the phenol compounds as intestinal antiseptics. By combining with the sulphates they deprive the body of the power of rendering harmless those putrefactive substances of which they cannot altogether prevent the formation.

This may also be the explanation of the value of sulphates in the treatment of certain intestinal diseases; they are not only aperient, but also antitoxic in their action.

In fact, the ratio $\frac{\text{ethereal sulphates}}{\text{simple sulphates}}$ gives a much surer indication of the existence or approach of an intoxication by aromatic bodies than qualitative tests for indican.

Normally this ratio is 1 in 20 to 1 in 10. It is sometimes high when little indican can be found in the urine, and low in the presence of marked indicanuria. Mackenzie Wallis finds that indican tends to disappear on standing, so that it is important to examine the urine quite fresh; therefore indicanuria is at best rather a fallacious guide to the recognition of an intestinal intoxication, but its persistent occurrence suggests careful investigation of the digestive system for visceroptosis and the like.

The discovery by Barger and Dale of diamines set free by putrefactive changes, which raise blood-pressure, confirms the general impression that intestinal putrefaction is a factor in the rise of blood-pressure in later life.

The other two food-stuffs may be held almost guiltless as a cause of intestinal intoxication. In fermentative dyspepsia carbohydrates may give rise to oxalic acid, causing oxaluria; more commonly they are a source of lactic acid, which is antagonistic to putrefaction. Fats will produce fatty acids as a result of bacterial action, but these will not produce toxic symptoms. The fatty acids associated with ketosis in diabetes, however, come largely from the fat in the food.

The case for the occurrence of an intoxication from the bowel by the normal or ordinary putrefactive products of food-digestion cannot be regarded as proven. Yet on this unstable foundation the most airy and far-reaching hypotheses have been reared. Herter attempted to place the matter on a sounder basis in his description of three types of chronic intestinal putrefaction:

1. *Indolic*, due to the *Bacillus coli*, and perhaps the *B. putrificus*. The commonest form is in marasmic, large-bellied children with chronic intestinal indigestion. Carbohydrates are not digested well, while proteins and fats are well borne. The subjects are sharp witted; they are intolerant of cold, and are easily fatigued. Indican and other ethereal sulphates are markedly increased in the urine. For treatment he advises that the carbohydrates should be restricted to well-cooked rice or biscuits. Milk should be peptonized for a time, and a moderate amount of finely-divided meat given. Gelatin may be useful, because it contains no tryptophan, the precursor of indol. A few rather generous meals are better than frequent feeding. High irrigation of the bowel may be beneficial.

I think we are all familiar with a vaguer condition of this type in adults also. They are the subjects of headaches; the tongue is furred; the breath is heavy or offensive; the stools are light in colour. They are liable to 'bilious attacks.' There is a marked indicanuria. Such persons may easily go on to suffer from the further *Bacillus coli* infections discussed in the next section.

2. *Butyric*, chiefly due to *B. aerogenes capsulatus*. The nascent hydrogen causes much reduction of the bile pigment, so that there is excess of urobilin. Addition of a strong solution of mercuric chloride to the fæces produces a red colour, which is more distinct on throwing the fæces into water. There is little or no indican in the urine. Indefinite invalidism may be the chief symptom. The subject is often sour-smelling; the epithelium of the tongue and mouth is seen to be desquamating. Hence the irritable condition of the alimentary canal, with the tendency to diarrhœa. Shreds of epithelium may be seen in the fæces. In advanced cases an extract of the fæces may be hæmolytic in action. At this stage anæmia comes on —first a diminution in the blood volume, then of the hæmoglobin, and then of the red corpuscles.

Though the symptoms in adults are usually latent or chronic, in infants the *B. aerogenes capsulatus* may be virulently pathogenic. I recall a child of three that died with symptoms of acute bronchitis. Some petechial hæmorrhages into the stomach roused my suspicions, and the heart's blood, lung, liver, and spleen were found by Dr. Gordon to yield the *Bacillus aerogenes capsulatus*, which, on injection into guinea-pigs, proved to be very virulent, causing death in twelve hours, with hæmorrhagic necrosis of the subcutaneous tissues.

3. *Combined Indolic and Butyric.*—Nervous symptoms occur relatively early. The subjects become invalided more rapidly than with either indolic putre-

faction or butyric fermentation separately. The outstanding features of the case are mental depression and muscular fatigue.

Specific Intestinal Intoxications.

These may apparently arise in one of three ways—

1. There may be alterations in the intestinal flora, so that bacteria can thrive which produce specific toxic substances.

2. The bacterial processes may spread up from the large to the small intestine.

3. Normal intestinal bacteria may pass into the blood in consequence of lowered resistance of the epithelium or lowered bactericidal power of the blood.

The *Bacillus coli communis* may be regarded as a normal inhabitant of the alimentary tract, but when it strays beyond its proper domain it may cause cholecystitis, gall-stones, cystitis, pyclonephritis, or phlebitis. Thus, according to Sidney Martin, the phlebitis of influenza is really due to a secondary infection by this organism. Such *B. coli* have a heightened virulence for animals. In this connection the premature appearance of the *Bacillus coli* in the intestines of bottle-fed children is important, because in early life the normal mucous membrane is more easily permeable by bacteria, while the intestinal flora should be less varied and less toxic. There is a parallel development of more putrefactive organisms and a higher resisting power. Therefore the *B. coli*, if

prematurely introduced into the infant's intestine, may prove virulently toxic. In a post-mortem examination I made of a premature child two days old, the only macroscopic lesions were hæmorrhages into the right lung, but the heart's blood was swarming with *B. coli.*

Another example of the way in which normal inhabitants of the bowel may intrude into damaged tissues with pathogenic results is seen in the engrafting of the *Streptococcus salivarius* or the *S. fæcalis* on to heart-valves already crippled by rheumatism, producing infective endocarditis.

In many instances it will be difficult, if not impossible, to draw a hard-and-fast line between intoxications and infections, because we cannot tell whether the microbe has been able to enter the portal blood-stream, and has become bacteriolyzed there, or whether the intestine has merely absorbed the toxins produced in the intestine. Indeed, we can sometimes recognize three stages in the same case—

1. Intestinal absorption of toxins only.

2. The organism in the portal blood, soluble toxins in the general circulation.

3. The organism in the general circulation—*i.e.*, septicæmia.

As an example of a disease that may be either an intoxication or an infection, we may take 'Louping-ill,' or paralytic chorea in sheep, because Hamilton's work on the subject is the model on which research will have to be carried out in man to establish the pathology of like conditions. Louping-ill is a terribly fatal disease

affecting sheep on the west coast of Scotland between the months of April and June. There are three stages—

1. The animal is apathetic, and staggers.

2. Spasmodic convulsions occur, which may go on to coma or to—

3. Flaccidity, with abolition of reflexes.

Sometimes there is diarrhœa with passage of blood. Recovery seldom, if ever, occurs. There may be excess of turbid and sometimes blood-stained peritoneal fluid, which contains a large, coarse-looking rod organism, with a great tendency to spore; and even clear peritoneal fluid showed the same organism on incubation in sealed tubes for twenty-four hours.

Injection of liquids containing spores reproduces the disease, and the same organism can be obtained from the walls or contents of the bowel. When the organism is injected subcutaneously, death takes place from acute toxic poisoning before the characteristic nervous symptoms can develop; when introduced by the alimentary canal, these are well developed. Hamilton bacteriolyzed the organism by the blood of sheep *in vitro*, filtered, and injected the filtrate subcutaneously, causing the characteristic symptoms. Thus an intoxication may occur, even though an infection has been prevented by the destruction of the microbe.

The cause of the periodicity of the disease appears to be that the blood is bacteriolytic to the organism at other seasons.

Immunity may be conferred by feeding an animal

on cultures during the period of the year that it is insusceptible, which recalls the immunity acquired to typhoid fever by the inhabitants of a district in which it is endemic.

I should like to emphasize the fundamental importance of these experiments, in which the method of infection is clearly worked out, and the line of successful treatment clearly laid down.

Horder has recorded an interesting example of the way in which the method of infection can be worked out in human beings. A boy, aged seven, had been playing in a field where the contents of a house privy were deposited. The next day he vomited and complained of abdominal pain. The temperature was intermittent, the stools contained mucus and blood, and he became jaundiced. On the twenty-sixth day the elder brother, aged twelve, was seized by an illness which began to run the same course. Cultures from the blood and urine were sterile. Cultures from the fæces were plated out, and agglutination tests were undertaken with the blood of both boys against the dominant strain of colon bacillus present in the fæces; clumping occurred readily. The conclusion was that the most probable cause of the portal infection was a virulent colon bacillus. As far as the general circulation was concerned, only a stage of intoxication had been reached, since the blood was sterile. A vaccine was prepared from this bacillus, and two doses given to each boy, with an interval of five days between the doses. Rapid improvement followed; and as the

cases were at different stages of their illness, the recovery could not be explained as the natural termination of the attack.

As I have deprecated indiscriminate reference to pyorrhœa to explain diseases of obscure causation, I should like to add that I have seen many cases of fever without physical signs traced to pyorrhœa, which have recovered on removing the offending teeth, perhaps with the aid of a vaccine prepared from them.

X-ray examination of the tooth sockets has proved a great help in recognition of this deep-seated septic absorption.

Microbic Cyanosis.—In 1902 Stokvis described cyanosis as a result of intestinal troubles. The abnormal colour was due to the presence of methæmoglobin in the red corpuscles. The patient had great intestinal irritation, clubbing of the fingers, deep cyanosis, and considerable albuminuria. After death it was discovered that he had suffered from parenchymatous nephritis, with ulcerative enteritis.

Van den Bergh found the connecting-link between the intestinal trouble and the resulting blood changes to lie in the presence of nitrites, which lead to the formation of methæmoglobin. He found that the condition would clear up in from twenty-four to forty-eight hours on a milk diet, but returned in four hours after an ordinary meal. He also described four cases of sulphæmoglobinæmia—*i.e.*, a sulphur compound of hæmoglobin, which in itself suggests an intestinal source for the intoxication.

Gibson described a case in a married lady, aged thirty-six, who had been cyanosed for two or three years. The face and hands were of a lavender hue, while the lips, ears, and nails were nearly as dark as bilberries. The spectroscope showed the band of methæmoglobin, while nitrites could be detected in the blood, fæces, and saliva. A coliform organism was isolated from the blood on one occasion only. Great improvement followed intestinal antisepsis, and methæmoglobin could no longer be found.

I had the opportunity of seeing the first case of sulphæmoglobinæmia recognized in this country, which was under the care of Dr. Samuel West at St. Bartholomew's Hospital.

An unmarried woman, aged thirty-seven, was admitted for debility and cyanosis. The skin was of a leaden hue, resembling that of silver staining. The colour was due to the blood, and not to deposited pigment, for on pressure the skin could be shown, when emptied of blood, to be of the normal hue. The fingers were not clubbed. I examined the blood spectroscopically in the circulation by holding the patient's hand in front of an electric light and pressing the web of the thumb between two glass slides until a convenient thickness was obtained. A spectrum closely similar to that of methæmoglobin was obtained, with a well-marked band in the red. I was at that time ignorant of Van den Bergh's work, and everyone regarded the case as one of methæmoglobinæmia. Drug habits were therefore suspected. These, how-

ever, could be excluded with an unusual degree of assurance. Her medical man stated that, except for occasional doses of bromide and iodide, he had given nothing more for a long time than a tonic of iron with arsenic. The patient lived in a remote part of the country, from which the nearest druggist's shop was some miles away; she could only have got drugs by post. But neither her family or the postman knew anything of her receiving such parcels. Moreover, during her stay in the hospital she certainly had no such drugs, yet the cyanosis persisted.

A more thorough examination of the blood by Wood Clarke revealed the fact that the bands were those of sulphæmoglobin. The urine contained less indol than usual—an interesting comment on the slight value to be attached to this body as evidence of an intestinal intoxication. The ethereal sulphates were greatly reduced. Nitrites were found in the urine. No increase in sulphuretted-hydrogen-forming organisms could be found in the intestine. A culture taken from the blood in the arm was sterile. Moreover, the long duration of the case was against the theory of an infection, and pointed rather to an intoxication.

Subsequently Mackenzie Wallis found in the mouth of this and four other patients with sulphæmoglobinæmia a nitrifying bacillus, which formed a strongly reducing substance. This substance, which was also present in the serum of all the patients, could reduce oxyhæmoglobin, an essential step in the formation of sulphæmoglobin. One case was apparently cured by

removal of the teeth and the use of an autogenous vaccine prepared from this nitrifying bacillus. The name 'microbic cyanosis' is therefore strictly applicable to the condition. These observations support the view I have already expressed that definite intestinal intoxications are due to abnormal pathogenic bacteria rather than to the ordinary products of putrefaction. Jamieson has recently reported (*Quarterly Journal of Medicine*, 1919, vol. xii., p. 81) a series of attacks of short duration in a patient, accompanied by enlargement of the spleen.

Hæmatoporphyrinuria.—The decomposition of the hæmoglobin molecule may be tabulated as follows:

- Hæmoglobin.
  - Hæmatin.
    - Hæmatoporphyrin.
    - Iron salt.
  - Histone.

Probably hæmatoporphyrin is normally converted into bilirubin by the liver.

A trace of hæmatoporphyrin is a normal constituent of urine, but under certain conditions this is largely increased in amount, such as in sulphonal, trional, and tetronal poisoning. But there are other groups of cases where such drugs can be excluded.

One group is congenital. The pigment may stain the bones, and even the enamel of the teeth. Sometimes the spleen is enlarged. Like certain other fluorescent pigments, hæmatoporphyrin increases the

sensitiveness of the skin to light, which probably accounts for the recurrent attacks of hydroa vacciniforme to which the subject is liable each summer.

The other group shows an acute onset with toxic symptoms, such as vomiting, thirst, anorexia, abdominal pain, and profound prostration. Ranking and Pardington described two such cases, and I had one under my care in which three attacks of this character had led to the suspicion of intestinal obstruction. Ascending paralysis has also been described. Monro has seen hæmatoporphyrinuria in periodic vomiting with acetonuria in a boy.

All these points are suspicious of an intestinal intoxication, and the suspicion is strengthened when we remember that hæmoglobin will break down into hæmatoporphyrin much more readily in the reduced state than when containing oxygen. Now Hurtley and Wood Clarke have shown that in the formation of sulphæmoglobin the blood pigment is first reduced, and then combines with the sulphur.

This suggests that in both cases some reducing agent is at work, and the intestinal symptoms point to the alimentary canal as its source, the liver becoming secondarily involved. It is interesting to compare this condition with methæmoglobinæmia, which may also be caused either by intestinal intoxication or by coal-tar drugs.

In the future many other conditions may be proved to be due to intestinal intoxication, but the evidence is not always convincing at present.

Hunter has laid great stress on oral, gastric, and intestinal sepsis as the cause of *pernicious anæmia.* There is a strong case for hæmolysis in the portal area in this disease. Now, the anærobic bacteria naturally present in the human intestine include some highly pathogenic members which under proper surroundings can produce marked hæmolysis. Ultimately we shall probably find that many of the obscure intestinal intoxications are due to anærobic bacteria.

Though *cirrhosis of the liver* occurs in alcoholic subjects, direct administration of alcohol experimentally leads to a fatty and not to a fibrotic change in that organ. Consequently the condition has been referred to impurities in the common alcoholic drink of the country. Thus in wine-drinking countries the potassium sulphate with which the *vin ordinaire* is plastered, and in whisky-drinking countries the fusel-oil, have been held responsible. Such wide differences of opinion make it all the more probable that the ingredient common to them all, the alcohol, is really the agent at work. Rolleston explains this dilemma by the view that alcoholic excess leads to a prolonged gastric catarrh, which, by lowering resistance, enables toxic substances to be absorbed from the bowel. Hamilton's suggestion, which harmonizes with this quite well, is that a microbe is absorbed from the intestine, bacteriolyzed in the portal blood, and its liberated toxins anchored on to the liver substance. This might occur in other than alcoholic subjects, and it certainly appears that we cannot explain all cases of multilobular

cirrhosis by alcoholism. The chronic peritonitis which produces the ascites in the later stages of cirrhosis means that ultimately the organisms as well as the toxins have been absorbed. Durham has shown that these organisms can always be found in the omentum although the ascetic fluid is sterile.

There is a growing opinion that many *chronic affections of the joints* are due to a chronic infection or intoxication. Either the alimentary or the genito-urinary tract may be the 'open door' by which the infective agent enters. And so it has come about that pyorrhœa alveolaris must be regarded as a potent cause of rheumatoid arthritis. Until this has been excluded, if necessary by an X-ray examination, other forms of treatment are a waste of time in this disease, but other septic foci must not be overlooked. *Tetany* is another condition which has been held to be due to a gastro-intestinal intoxication. Its occurrence in rickets, with gastro-intestinal disturbances, in typhoid fever, and after lavage for dilated stomach is certainly suggestive. Its association with the parathyroids has already been discussed.

But I do not wish to multiply the list of diseases for which an intestinal intoxication might be held responsible. For the present this is mere speculation. We may lay down the following conclusions as to etiology:

1. There is no satisfactory proof of intoxication by the ordinary disintegration products of digestion.

2. Putrefactive processes mainly affect the aromatic

—*i.e.*, benzene—groups of the protein molecule; there is no conclusive evidence that these can lead to symptoms of intoxication. Occasionally the sulphur in the protein molecule appears to be able to cause chemical changes in the hæmoglobin, with resulting cyanosis. But here, too, an abnormal bacterial agent is apparently at work.

3. It is often difficult, if not impossible, to draw a hard-and-fast line between an infection and an intoxication. The microbe may sometimes be able to establish itself in the blood-stream, thereby producing an infection, while sometimes it is rapidly destroyed by the blood, but it is, nevertheless, able to disseminate its soluble toxins in sufficient quantity to produce symptoms.

4. I believe we shall ultimately be able to refer all the real intestinal intoxications to the presence of actively pathogenic bacteria among the ordinary saprophytes of the intestine.

Treatment.

The indications are as follows:

1. *Avoidance of Putrefactive Contamination of Food.*—All food should be cooked as far as practicable. Cheese, especially the riper varieties, should be avoided. All fruit should be peeled. Careful attention must be paid to the teeth, since anærobic bacteria lurk in the interstices, and these are a great factor in intestinal putrefaction.

2. *Promotion of Prompt Digestion and Absorption.*—Here again attention to the teeth is important, to allow of proper mastication. Hydrochloric acid should be given if it be deficient in the gastric juice. But in the cases of butyric fermentation diastatic ferments are better than hydrochloric acid, which is not well borne. Pepper, mustard, excess of salt, vinegar, and lemon, are irritant to these patients. Demulcent drinks are indicated. The butyric type need careful preparation for a generous diet. Emotional irritability or mental depression, increase in the ethereal sulphates of the urine, of gas-producing bacilli in the stools, or of intestinal flatulence, are signs that the food should be reduced. Intestinal flatulence especially indicates reduction in the amount of carbohydrates. If there be atonic dilatation of the stomach, lavage may be employed, but nervous causes should be enquired into. Rest after meals should be enjoined.

3. *Limitations of the Number of Bacteria.*—Micro-organisms form one-third of the total solids of the stools, though the greater number of these are dead. Intestinal antisepsis is a counsel of perfection, and at present we are scarcely prepared to accept Metchnikoff's dictum that senile changes are the result of an intoxication from the large bowel, so that it is hardly likely that we shall attempt intestinal antisepsis as a routine measure. Occasions have doubtless arisen in the experience of all when it has appeared desirable to make the attempt, though a sense of despair was felt in trying to accomplish it. Calomel in small and

divided doses, followed by a saline purge next morning, is a time-honoured method of attempting to effect this. However useful this may be to start treatment, we must beware of a routine use of strong purgatives to this end, for, by removing the superficial epithelium of the bowel, they may facilitate septic absorption. After a preliminary dose of calomel, my custom is to give 3 minims of cyllin medical or 2 minims of izal in capsules three times a day for not more than four days. If continued longer than this, it is apt to cause irritative symptoms. After that naphthalene tetrachloride in 5 or 10 grain doses should be given three or four times a day. As it is insoluble and cannot, therefore, he absorbed, it does not produce any toxic symptoms. Ten grains of sulphocarbolate of soda or of salol may be tried; they are not always a success, and I have suggested the reason; but β-naphthol in 5-grain doses in cachets sometimes gives good results. A cachet containing 3 grains of benzo-naphthol with $\frac{1}{4}$ grain of menthol is useful where there is much flatulence. Thymol, manganese dioxide, hydrogen peroxide and ichthyol, have all been recommended, by various observers. Paraffin is not only aperient, but inhibits the growth of intestinal bacteria to some extent.

Treatment by Lactic Acid Ferments.—Metchnikoff has suggested another way of attacking this difficult problem. Instead of attempting to render the bowel aseptic, he advises the introduction of other organisms which are antagonistic to the growth of the putrefac-

tive bacteria. These are the lactic-acid-producing organisms. Soured milk has long been a staple article of diet among Oriental people, and enjoys a high repute as a hygienic measure. James Riley, in 1854, claimed that it had an extraordinary effect in promoting longevity. He asserted that wandering Arabs, subsisting almost entirely on the fresh or soured milk of camels, lived for two or three hundred years! It may be added that Riley was an American.

Bulgarian 'yahourth,' or 'yoghourt,' is milk soured by the most powerful lactic-acid-producing bacillus known. The commercial product contains a diplococcus and a strepto-bacillus also, but preparations of selected lactic ferments can be obtained.

The ridiculous way in which this lactic acid treatment has been boomed as a panacea has naturally excited a prejudice against it. In the first place, it is certain that in many instances no living Bulgarian bacilli have been taken at all; in the second, it has been used in totally unsuitable cases. Tablets of all kinds should be abandoned as a means of administering these organisms, which are too delicate to be able to survive such handling with any degree of certainty. Only fluid cultures or the milk actually soured by the bacilli should be employed. As to the selection of cases, the treatment can only be expected to be beneficial where there is definite evidence of increased putrefaction of proteins. Morbid conditions of the intestine may also be due to abnormal fermentation of the carbohydrates; in such cases the lactic acid treatment will

only do harm. The reaction of the fæces will be a guide; if they are acid, this treatment is unsuitable; if they are alkaline at first, but yield a fair quantity of gas in the fermentation tube, showing an acid reaction after, the treatment will probably be unsuccessful. Good results can only be expected in the cases where the fresh fæces are alkaline and remain alkaline after twenty-four hours, yielding hardly any gas to the fermentation tube.

4. Guelpa's method of detoxication by a combination of fasting, purgation, and diuresis has had excellent results claimed for it by various observers. The method is as follows: For three or four days, and sometimes longer, a bottle of purgative water is taken. Guelpa recommends that the following mixture should be dissolved in half a litre of boiling water:

Magnesium citrate	dr. x.
Calcined magnesia	gr. xxx.
Sodium chloride	gr. xv.
Essence of citron	♏ x.

Half of this to be taken in the morning quite hot, and the rest to be taken ten minutes later. During these days no food of any sort is taken, but a mineral water, such as Evian, is drunk freely, or a tisane, such as Tilleul, sweetened with a little saccharin. As after all fasting procedures, ordinary diet should only be cautiously resumed.

5. *Plombières Douches* may be tried. It is important that they should not be given more frequently than

three times a week, and that not more than 18 inches of pressure should be used. The treatment should not be continued more than about three weeks. If these precautions are not observed, mucous colitis is almost certain to be produced.

6. *Mechanical Supports.*—When there is definite visceroptosis, much help may be derived from a well-fitting abdominal support. In my opinion, Curtis's is the best.

7. *Surgical Procedures*, such as irrigation of the colon through an appendicostomy wound, colopexy, short-circuiting, and even excision of the colon, have all been advised. They can seldom be required, and should only be considered when all medical means have failed.

8. *Vaccine Treatment of Intestinal Intoxications.*—The most rational procedure is to try and isolate the microbe responsible, if possible, but the results have been rather disappointing. If a blood culture be sterile, a plate culture may be made from the stools, and the effect of the patient's blood in agglutinating or destroying the more definitely pathogenic organism tried. If we get a positive reaction with one or more of these, a vaccine should be prepared from such organisms. If it benefits the patients, we shall at once have established the fact that the case is really one of an intoxication, and have initiated the rational treatment for it. In the case of *Bacillus coli* vaccines, Sidney Martin advises beginning cautiously with small doses, such as one to four million.

At present it is not practicable to work out cases in

ordinary practice in this way, but we may look forward to a time when we shall be able to correlate certain definite signs and symptoms with certain distinctive microbes. The lines along which advance may be made will be evident. Casually testing the urine for indican is not sufficient for diagnosis, nor does purgation and extraction of the teeth comprehend the methods of treatment.

CHAPTER XII

IRREGULAR ACTION OF THE HEART

During the last few years much attention has been given to the study of cardiac irregularities in consequence of the introduction of Mackenzie's polygraph and Einthoven's string galvanometer, which have rendered the recognition of the various types possible. This is a gain, for the interest taken in cardiac murmurs had rather distracted attention from the cardiac rhythm. But our aim in treatment is to restore a normal rhythm; we cannot repair a valve. After all, the only value of a murmur is that it enables us to form an opinion as to the condition of the valves, and deduce the probable effect upon the heart muscle.

It would be unfortunate, though not surprising, if this activity in research created the impression that the subject had become too complex for any but specialists to appreciate. Although it requires special training to obtain or to interpret a curve obtained with the polygraph or galvanometer, certain simple main conclusions have been reached which affect everyday practice. I propose to describe the chief types of irregularity, to explain their production and significance,

and to show how far their recognition is now possible by means of the associated signs and symptoms, without the aid of elaborate apparatus.

It is to Gaskell that we owe our fundamental conceptions of cardiac rhythm. Here, as in his pioneer work on the sympathetic nervous system, his philosophical insight enabled him to lay the foundations so well and truly that it has only been left to others to build along his lines. After more than twenty years this work was applied to clinical medicine, with excellent results.

Previous to Gaskell, physiologists had referred the rhythm of the heart to the intracardiac ganglia. Bernstein had shown that if the ventricle of the frog's heart were 'physiologically disconnected' by crushing the auriculo-ventricular junction with a fine pair of wire forceps, it remained quiescent, while the rest, which contained ganglion cells, continued to beat. But Gaskell showed that if the intracardiac pressure were raised by ligaturing the aortæ, the ventricle would beat rhythmically once more.

In the tortoise's heart he was able to divide the septal nerve which passes between the two intracardiac ganglia without disturbing the rhythm; and by a series of interdigitating cuts in the auricular substance he compelled the wave of contraction to pass along a zigzag strip of muscle between the sinus venosus and ventricle, though all nerves must have been divided. Finally, by warming the ventricle and cooling the sinus, he was able to alter the relative excitability of the two

ends of the heart so much that a reversed rhythm was produced. His conclusion was that rhythm was an inherent property of the cardiac muscle, and did not depend on the intracardiac ganglia. The beat normally began at the sinus, because here the muscle was of a more embryonic character, while the ventricular muscle was the most differentiated.

He also showed a point which has now become of great practical importance. If the bridge of auricular muscle be made too narrow by cutting, a 'block' is established on the course of the muscle wave, so that not every beat can pass over into the ventricle, but only alternate waves, or one out of every three, according to the width of the bridge. But after inhibiting the heart by stimulation of the vagus, the muscle accumulates enough energy during the enforced rest to enable it to convey every beat across the narrow bridge. On the other hand, in the period of comparative exhaustion following sympathetic stimulation, the conductivity is lowered, so that fewer beats can pass over. An adequate strand of conducting tissue is essential to the due propagation of the wave of contraction along the cardiac tube.

Stanley Kent, in 1893, was the first to apply these results to the mammalian heart by proving the existence of muscular continuity between auricle and ventricle. His, and then Tawara, worked out the nature of the connecting band or 'auriculo-ventricular bundle,' as it is now called, in much greater detail. It begins near the anterior edge of the right coronary

vein, and then passes forward on the right side of the auricular septum below the foramen ovale. Just below the insertion of the median flap of the tricuspid valve this bundle forms a knot-like thickening, the auriculo-ventricular node. From this knot a process arises which penetrates the fibrous septum, and runs along just below the pars membranacea of the septum, dividing into two main branches, which pass obliquely downwards, one on either side of the septum under the endocardium. So far these fibres do not blend with those of the ordinary cardiac muscle, being enclosed in a separate fibrous sheath; but when they reach the papillary muscles they divide into a large number of branches, some of which enter the papillary muscles, while others pass on beyond them and follow the course of the small trabeculæ to the parietal wall, where they branch upwards and downwards under the endocardium lining the whole inner surface of the cavity of the ventricle, to fuse everywhere with the ordinary cardiac muscle fibres.

The heart muscle of elderly people being of a brownish colour, the left main branch, with its two secondary branches, stands out very plainly on account of its rather greyish-white colour, but it can be recognized with practice even in the hearts of younger individuals. The node is made up of fine, pale, branching fibres with faint striation, which in some respects resemble embryonic muscle fibres. The fibres interlace and fuse with one another, thus contrasting with the elongated parallel arrangement of the rest of the

cardiac muscle. The branches and terminal filaments of the bundle resemble the fibres, described in 1845 by Purkinje, in the subendocardial layers of the sheep's ventricle. Morphologically and histologically these fibres represent the invaginated portion of the primitive tube from which the complex heart of the mammal is built up.

But if these primitive fibres are the conducting strand along which the wave of cardiac contraction passes, we should expect to find them at the junction of the great veins with the heart, for this is where the wave starts. Keith and Flack found a remnant of primitive fibres persisting at the sino-auricular junction, in close connection with the vagus and sympathetic nerves, and having a special arterial supply. This is called the 'sino-auricular node.' Here the dominating rhythm of the heart normally arises, and here it may readily be modified by those extrinsic nerves which are known to influence it.

Between the sino-auricular node and the auriculo-ventricular bundle there appears to be no strand of specialized tissue, though one observer, Thorel, claims to have found one. As we pass from the lower to the higher vertebrates, the primitive tissue becomes reduced in amount, and more concentrated in position; a single strand of communicating muscle fibre is peculiar to the mammalian heart. With this reduction the heart becomes less automatic in its action, and more in subjection to the central nervous system. Indeed, the nodes are extremely intimate neuro-mus-

cular contacts. They have even been compared to the muscle-spindles of voluntary muscles—*i.e.*, sensory rather than motor structures. Without going as far as this, we may admit that the bundle is not only a conducting, but a co-ordinating mechanism. Keith found in a case of heart-block of eighteen years' standing that the bundle below the site of destruction was quite healthy. If it were merely a conducting bundle, it must have atrophied. As it did not, it must have some further function: it can create and co-ordinate as well as conduct a stimulus.

The anatomical and experimental evidence is in favour of extending Gaskell's conceptions, slightly modified, to the mammalian heart. Hering was able to produce a complete stoppage of the supraventricular parts of the heart by a cut made at the sino-auricular junction; while Erlanger has shown experimentally that it is possible, by interfering with the auriculo-ventricular bundle, to reproduce the phenomena described by Gaskell in the tortoise's heart, and many of the forms of irregularity met with clinically. A clamp was devised in which a small piece of tissue, including the bundle, could be subjected to varying degrees of compression while preserving its normal relations. With very slight compression there was merely a lengthening of the normal pause between the auricular and ventricular contractions. These intersystolic periods, however, usually lengthen until eventually the ventricles fail to respond to one of the excitation waves. In the next cycle the intersystolic

period, owing to the increased excitability of the rested ventricular muscle, is unusually brief. In succeeding cycles it again progressively lengthens until the ventricles again fail to contract.

On tightening still more, further stages of heart-block occur, the auricles giving three or four beats to each ventricular contraction. When efficient waves get through from the auricles at longer intervals, the ventricles begin to beat independently. Thus a complete dissociation of the auricular and ventricular rhythm results.

Before discussing the clinical equivalents of these phenomena, it will be well to consider a little more closely the physiological peculiarities of cardiac muscle. The following facts throw some light on its rhythmical power:

1. If a resting cardiac muscle be stimulated by a series of shocks, a progressive improvement is seen in the first few beats, producing the so-called *staircase.* Each beat acts as a stimulus to the next, so that a rhythm, once started, tends to be maintained. This is apparently due to the stimulating effect of the carbon dioxide produced by the muscle. Carbon dioxide is thus a stimulant both to the heart and the respiratory centre, providing in this way for its own removal.

2. *All shocks are maximal* to the cardiac muscle—that is to say, whether a large or small shock be given, the response is the same, the muscle giving the best beat it is capable of at that moment. This is not a

contradiction of the previous statement; the staircase would be seen just the same whether large or small shocks, or shocks of varying strength, were used. As long as the stimulus is effective the muscle gives the same response to each.

3. Cardiac muscle has a *long refractory period.* If a shock be sent in just after a beat has begun, the stimulus is ignored; if it be sent in a little later, a small beat is given after the ordinary one; but the heart makes up for this by a longer pause, so that the third beat does not start till the usual time. It is therefore impossible to throw heart muscle into tetanus.

These facts can be partly explained on the analogy of a gun. When the gun is loaded, it does not matter whether much or little force is expended in the pulling of the trigger, the whole charge is fired off; and when the charge has been fired off, it does not matter how forcibly the trigger is pulled, there is no response. The analogy fails in that we are able to get a small contraction when the fibre has partly recharged itself. All this points to an elaboration of contractile material in the muscle substance, which is 'fired off' as soon as enough is accumulated. Normally the charge is fired off by the train laid in the auriculo-ventricular bundle.

We do not know at present what the charge is composed of, but we do know that ionized salts play a large part in its elaboration. For, whereas dialyzed serum will not maintain cardiac rhythm, a saline fluid, such as Ringer's, which contains salts of sodium, potassium,

and calcium, is highly efficient for this purpose. If potassium be omitted the heart does not relax properly, while if calcium be left out systole becomes imperfect. And Locke has shown that the addition of dextrose and oxygen to Ringer's fluid makes it a remarkably efficient medium for maintaining rhythmical contractions in an excised heart. In the presence of these substances, then, the heart is able to keep up a supply of its contractile material.

This is not really incompatible with Carlson's ideas. According to him, the peculiarities of cardiac contractions are due to the heart wall being an intimate blend of muscle and nerve. His conclusions were reached by studying the contractions of the heart of *Limulus*, or king-crab. Here the muscular and nervous elements are anatomically separable, and the muscle is found to approximate in its reactions to those of ordinary muscle. And Rohde found that on perfusing chloral hydrate through the mammalian heart, a stage was reached at which the heart responded to direct stimulation like ordinary muscle. It was then readily tetanized, the characteristic refractory period was not in evidence, and the heart responded to stimuli of gradually increasing strength with contractions of gradually increasing amplitude. His interpretation was that chloral had accomplished pharmacologically the severance of the nervous and muscular elements, which can be performed anatomically in *Limulus*. If we regard the cardiac wall as neuro-muscular in structure, it does not dispose of the argument that the rhythm is

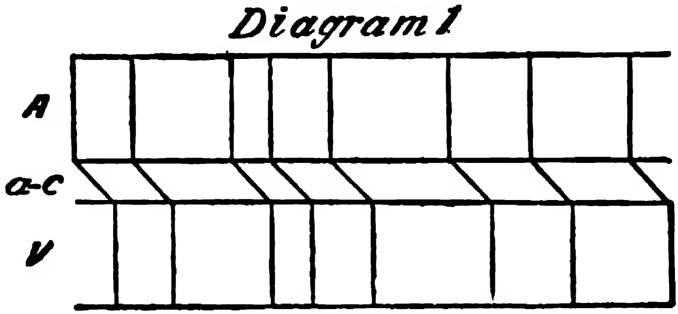
independent of the macroscopic ganglia, but is conducted along a strand of embryonic fibres which represent the remains of the primitive cardiac tube.

Types of Disturbed Cardiac Rhythm.

We can classify the principal types of cardiac irregularity in terms of disturbed function of this primitive cardiac tube. If the rhythm be initiated irregularly at the sinus venosus, we have the type known as *sinus irregularity;* an abnormal stimulation of the tube at some point below the sinus results in a smaller premature contraction or *extra-systole.* If the contraction of the auricle between the sino-auricular node and the auriculo-ventricular bundle is disorderly, we have *auricular fibrillation.* A diminution in the conducting power of the bundle prevents each contraction of the auricles from being followed by one of the ventricles, *heart-block.* Finally, owing to exhaustion of contractility the beats may vary in strength, *pulsus alternans.* Most forms of irregularity can be explained as due to one or more of these conditions.

1. **Sinus Irregularity.**—The remains of the sinus venosus at the entrance of the great veins is the normal 'pacemaker' of the heart and sets the rhythm. In sinus irregularity the rhythm is initiated at the normal place, but not at the normal time. Once the wave of contraction is started it is propagated quite normally. The duration of systole remains constant, but the diastolic intervals vary. As the pulse quickens

it is the diastolic intervals that are encroached on, so that this type of irregularity tends to disappear as the heart quickens—as, for instance, in fever or exercise. On the other hand, it is apt to appear for the first time, or to reappear as the heart slows down after a febrile attack. Windle has noticed that it is common in children in such circumstances. The dog is very



SINUS IRREGULARITY.

A represents the auricular beat as determined by the jugular pulse. *V* represents the ventricular beat as determined by the carotid pulse. *a-c* represents the interval taken up in the passage of the impulse along the auriculo-ventricular bundle from auricle to ventricle. In sinus irregularity the inception of the rhythm occurs at irregular intervals, but each beat, when started, is carried out in a regular manner.

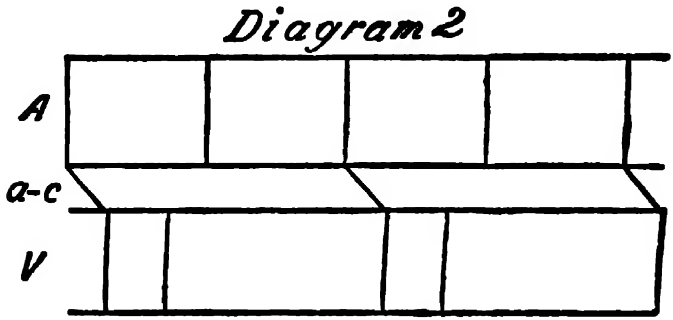
liable to this form of irregularity, which disappears after section of the vagus. It is therefore attributed to vagal irritation—a view supported by the fact that when the vagus is unduly irritable, sinus irregularity can be induced reflexly by swallowing or by hurried respirations—two acts in which the sensory branches of the vagus are stimulated—and by the fact that atropin temporarily abolishes it.

Sinus irregularity can be recognized by the fact that though the pulse-rate is varying, usually with respiration, the beats are equal in strength, while on auscultation the interval between the first and second sounds is constant. It is met with in healthy people as well as in neurasthenics. Mackenzie calls it the juvenile type of irregularity, and even considers its presence a sign that the myocardium is not impaired. It does not cause any real inconvenience, and is generally detected merely by examination. Its recognition is important simply that undue significance may not be attached to it. In short, an irregularity that disappears with exercise or with a rise of temperature need not trouble us. It is true that it may occur in cerebral diseases, such as tuberculous meningitis, but its presence does not affect the gravity of the condition in any way.

2. **Extra-Systoles.**—*Premature contractions of the auricle, or more usually of the ventricle, in response to a stimulus from some other portion of the heart than the sino-auricular node, but where otherwise the fundamental rhythm is maintained* (Mackenzie).

When a stimulus is initiated at some other part of the heart than the sino-auricular node a premature contraction will occur, and as the heart has not had time to accumulate enough contractile material, this beat will be smaller than normal, and, for a similar reason, it will be followed by a longer pause. This disturbance of rhythm constitutes the extra-systole, and usually involves the ventricle alone, though it may

occasionally implicate the auricle. It had been produced experimentally many years before its clinical counterpart was known. As was shown experimentally by Marey, and clinically by Lewis, the fundamental heart-rhythm is not disturbed by an occasional extra-systole; the next beat after it occurs at the proper time. It can be detected by the pre-



EXTRA-SYSTOLES.

Note that the auricular beats are regular, but that a premature ventricular beat occurs after the normal one. The next auricular beat, therefore, reaches the ventricle during the refractory period, and consequently is not followed by a ventricular contraction. The letters have the same significance as in the former diagram.

mature cardiac impulse followed by an abnormally long pause. On auscultation the regular sequence of the heart sounds is occasionally interrupted by two sharp sounds, or only one may be heard if the beat is feeble, followed by a long pause. The premature beat may not reach the wrist, because the contraction was not forcible enough to open the aortic valves. On examining the venous pulse in the neck while auscultating, it

may be noted that a large auricular wave comes just *after* the premature beat of the ventricles. This is due to the fact that the auricular rhythm occurring at the normal time has to attempt to drive blood into a ventricle already in systole, and failing to do this a larger volume of blood is driven back into the great veins. The chief sensation of which the patient complains is the long pause after the extra-systole, 'as if the heart had stopped,' or a 'thud' which accompanies the beat following the pause. What patients term 'palpitations' are usually extra-systoles.

Too much importance need not be attached to this form of irregularity. Mackenzie calls it the adult type of irregularity and says: 'I have followed cases for many years, and watched them pass through seasons of sickness and stress, and have seen no reason to attach any serious import to this symptom.' Lewis takes a more guarded view when he says: 'In themselves premature beats cannot be regarded as evidences of serious involvement of the heart-muscle, although such involvement is often found in conjunction with them.' Thus in a syphilitic, or if the blood-pressure is persistently raised, they may have a more serious significance, and graver irregularities, such as heart-block, may ensue. At first sight extra-systole seems diametrically opposed to heart-block, being due to increased irritability of the auriculo-ventricular bundle instead of diminished conductivity. But it has been found both experimentally and clinically that slight lesions

of the bundle may cause extra-systoles by stimulating it, while severer lesions may obstruct the conduction of a wave through it. Tobacco, digitalis, and digestive disturbances may all excite extra-systoles. They are more frequent, or, at any rate, the patient is more conscious of them, after food. Bromides in a digestive mixture may afford considerable relief.

Paroxysmal tachycardia is due to the less common condition of extra-systoles starting in the auricles. Although this does not strictly constitute irregularity except when the paroxysms last but a few seconds, it will be convenient to consider it here with the conditions to which it is so closely allied. Lewis (*Lancet*, 1912, ii., p. 1418) describes the features of a simple tachycardia such as occurs in exophthalmic goitre, pulmonary tuberculosis, infective conditions, and alcoholism, as follows: The pulse-rate falls during rest or recumbency, rising to the original rate on standing up again; it is enhanced by exercise, emotion, and the like; the electro-cardiogram is of the normal type, and the rapidity is gradual in onset and termination. This simple tachycardia should never, in the absence of other signs, suggest a cardiac lesion.

There are pathological types of tachycardia, on the other hand, which appear and disappear abruptly, and are uninfluenced by posture and exercise. In these the auricular portion of the electro-cardiogram shows a decided departure from the normal. This is due to an irritable focus in the auricle, and the auricular

extra-systoles are initiated there, passing onwards to the ventricle as usual, but *backwards* to the entrance of the great veins, thus inverting the auricular wave in the electro-cardiogram. Such a tachycardia rarely, if ever, produces contractions more frequently than 200 times a minute.

Attacks may be precipitated by exertion, emotion, flatulence, and the assumption of certain postures. Usually the only symptom is the rapid fluttering action of the heart, but in the more severe cases anginal symptoms and venous congestion may be present. Usually these abate quickly on cessation of the tachycardia, but fatal heart exhaustion has occasionally followed. Yet Lewis, with his exceptional experience, has not met with a fatal case, so we are justified in reassuring the patient. The spontaneous ending of paroxysmal tachycardia has led to various forms of treatment being credited, without justification, with producing the desired effect. A careful search should be made for any septic focus, a firm abdominal binder should be worn, and the application of an ice-bag to the precordium should be tried. Some patients have found for themselves that deep respirations or the adoption of a certain attitude, such as lying supine, affords relief.

Lewis distinguishes between this and a condition of '*auricular flutter*,' in which the auricular beat may rise as high as 350 a minute, but, as may be imagined, the ventricle can rarely keep up such a pace.

It may respond to every second or fourth auricular beat, or it may respond unevenly, producing obvious irregularity. His reasons for separating 'auricular flutter' from simple paroxysmal tachycardia are that the former may be forced by the administration of digitalis into auricular fibrillation, and that it is almost invariably associated with heart-block. But probably no hard-and-fast line can be drawn, flutter representing the more extreme grade of auricular extra-systoles, and therefore being more likely to produce an exhaustion of the auricle. When the tachycardia lasts for weeks or months, it is probably due to flutter. This condition is much more responsive to digitalis or strophanthus in full doses than the ordinary paroxysmal form, in which all remedies are uncertain.

8. **Auricular Fibrillation.**—*Interference with the passage of the wave from sinus to ventricle owing to irregular and inadequate contractions in the auricle.*

This is the irregularity seen in the later stages of mitral disease, especially mitral stenosis. Mackenzie has called attention to the way in which the typical crescendo presystolic murmur may suddenly vanish. A diastolic murmur, diminuendo in character, may be present, but its method of production is different. The crescendo murmur is due to auricular contraction, while the diastolic murmur is due to the blood which has been stored up in the auricle during ventricular systole flowing through a constricted orifice as soon as the ventricle passes into diastole. The former is

an active process, the latter is passive. At the same time the jugular pulse changes in character, presenting no evidence of an auricular contraction in the normal period.

Lewis found, by Einthoven's string galvanometer, that the ordinary wave of auricular systole is replaced by a number of very fine waves with a frequency of 200 to 300 oscillations a minute. Probably the overstretched muscle of the auricle with its obstructed outflow has become incapable of orderly contraction. This is supported by Lewis's observation that a rise of venous pressure produced by squeezing the abdomen may produce a paroxysm of auricular fibrillation, and by the fact that when auricular fibrillation is experimentally produced in the dog the auricle is seen to be 'ballooned.' The condition is also seen in arteriosclerosis, where degeneration of the coronary arteries impairs the blood-supply to the auricular muscle, and in Graves' disease. In each instance the auricular muscle is rendered more irritable but less effective. Both in auricular flutter and auricular fibrillation 'circus movements' are set up. The contractile wave continually passes over the auricular muscle, following a regular course in flutter and an irregular one in fibrillation. In the latter the stimulus, therefore, reaches the auriculo-ventricular bundle in a rapid and highly irregular rhythm, to which the ventricles can respond only in an irregular manner.

Auricular fibrillation can generally be recognized even without special apparatus by the following points:

(1) The pulse is completely irregular. There is no relation between the size and the strength of the beats and the preceding diastolic pauses, such as is found, for instance, with extra-systoles. (2) The veins in the neck are distended, causing a feeling of fulness, and the only large wave seen in them is synchronous with ventricular systole. (3) The disappearance of the typical presystolic murmur of mitral stenosis. (4) With the onset of auricular fibrillation the subjective symptoms become increased. Anginal pain, a fluttering sensation, faintness, pallor, and dyspnœa with orthopnœa are common. If they occur suddenly with an irregular pulse, they are almost always due to fibrillation.

In consequence of the rapid disorderly rhythm imposed on them, the ventricles are placed at a great mechanical disadvantage, and it is to this that the serious symptoms are due. Fibrillation plays an important part in the ultimate breakdown of the heart. If the ventricular rhythm can be made slower and more regular, enough blood can be aspirated from the auricles into the ventricles for the purposes of the circulation, even though the former remain in their state of paralytic distension. The action of digitalis is more successful in auricular fibrillation than in any other class of case, and a few doses may change the condition from one of acute distress to one of comparative comfort. This is apparently due to its depressing effect on conductivity, producing, in fact, a mild degree of heart-block, so that the auriculo-ventricular bundle ignores a large number of the

irregular stimuli it receives from the fibrillating auricle. It is best to give it in full doses of 15 minims four-hourly for a time. In Mackenzie's opinion there is no risk in doing this, as the first toxic action of the drug is headache or nausea and vomiting, which indicates reduction of the dose.

Of late the plan of rapid digitalization has been sometimes adopted in urgent cases. Fraser recommends giving three doses at six-hourly intervals, the first being 1½ drachms, the second 1 drachm, and the third ½ drachm of the tincture. Then there should be an interval of two to three days without medicine, after which ordinary doses of digitalis are given. When it has exerted its steadying effect on the rhythm, it can be reduced to the smallest dose sufficient to maintain the effect. The appearance of coupled beats is a sign to stop digitalis altogether for a time. The influence of the drug is much less if there is fever, especially if the fever is due to something which infects the heart-muscle. Of this a recurrence of rheumatism is a good example. Its action is less marked in the cardio-sclerotic cases, because there is generally more degeneration of the myocardium. It will be noted that digitalis does not strike at the root of the mischief; it merely checks its effects. In quinidine, however, we now have a drug which can frequently control the circus movements by lengthening the refractory period and slowing the conduction of the excitation wave from point to point in the muscle. Thus it restores a normal auricular rhythm. Its use

is not free from risk. Headache, nausea, vomiting, diarrhœa, and abdominal pain are not uncommon, but may pass off without reduction of the dose. Papular eruptions, visual disturbances, faintness, and distress have been recorded. A more serious drawback is its liability to produce embolism, particularly cerebral embolism, the restoration of auricular rhythm tending to dislodge clots from a previously stagnant cavity.

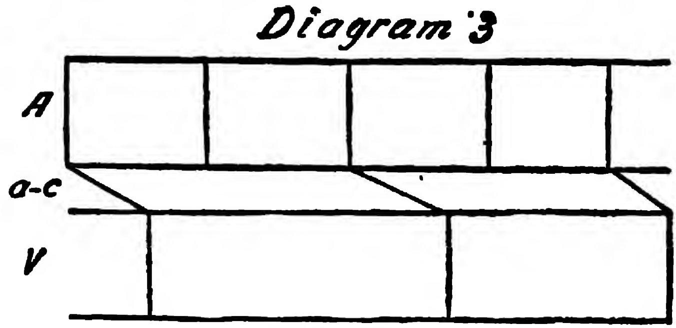
The dose usually recommended is 5 grains of quinidine sulphate six-hourly, increasing up to 7-grain doses, and then gradually reducing to 5 grains twice a day. But I have generally started with smaller doses than these, and it is always well to give a trial dose of 2 to 3 grains as a precaution against idiosyncrasy for it. Even when a normal rhythm has been restored a dose of 3 grains twice a day should be given over long periods to prevent relapse. The drug has been recommended for paroxysmal tachycardia, and I have used it with success in the auricular extra-systoles of exophthalmic goitre. But it will not prove a success either in this or in the auricular fibrillation of exophthalmic goitre as long as a toxic factor is present.

4. **Heart-Block.**—*Every auricular contraction is not followed by a ventricular contraction.*

Heart-block may be: (1) *Complete.* The rhythms of the auricle and ventricle are then entirely independent. (2) *Incomplete.* Then the conductivity of the auriculo-ventricular bundle is so impaired that one out of every two or three auricular beats is unable to initiate a ventricular beat. The lengthening of the *a-c* interval

before the dropping of a beat occurs is evidence of the difficulty that the wave of contraction encounters.

The features of heart-block are: (*a*) Slow pulse, at first paroxysmal, but tending to become permanent. The commonest rate is 30 a minute, but 20 or even as low as 6 have been observed. (*b*) The auricular contractions, as evidenced by the wave in the jugular vein, remain approximately normal, however, and



HEART-BLOCK.

Note the lengthened *a-c* interval, also that each auricular beat is not followed by a ventricular contraction. The letters have the same significance as in the former diagrams.

even by inspection of the neck it may be possible to make out that every contraction of the auricle is not followed by a ventricular contraction. (*c*) Attacks of vertigo, syncope, or epileptiform convulsions, in the severer cases.

The combination of slow pulse, and epileptiform convulsions has been known since the middle of last

century as Stokes-Adams disease, but its significance and the method of its production have only been recognized more recently. The anatomical changes found point strongly to the conclusion that the cause is a lesion of the auriculo-ventricular bundle, the cerebral symptoms being due to anæmia of the brain resulting from the defective circulation.

The following are some of the principal changes that have been found: Gummata (Handford, Keith and Miller); anæmic necrosis consequent on thrombosis of the nutrient arteries (Jellick, Cooper, and Ophuls); fibrosis (Barr, who, however, does not admit the significance of this; Schmoll, G. A. Gibson, A. G. Gibson); new growth (Sendler, Luce); atheroma (Stengel, Aschoff); fatty infiltration (Aschoff). That similar symptoms can be produced by pathological conditions so diverse supports the idea that the one feature common to them all—*i.e.*, interference with the conducting bundle—is the essential cause.

Temporary heart-block has also been described in acute rheumatism and influenza. This is probably due to the bundle becoming involved in the inflammatory lesions of the myocardium, which are by no means uncommon in rheumatism and septic states. Recovery may be complete, or fibrosis may follow, producing organic changes in the bundle in later life.

Heart-block has been observed in asphyxial conditions, even after both vagi have been cut. Lewis and Mathison believe that the lactic acid resulting from oxygen starvation poisons the conducting tissues. It

has also been excited by digitalis, aconitine, physostigmin, adrenalin, squills, and strophanthus, but apparently in all these cases there was impaired conductivity before the drug was given.

The following case, under my care, exemplifies the clinical features of this disease:

A man, aged thirty-nine, was admitted into hospital for numbness of the extremities and headache. There was nothing of importance in his past or family history. The heart-sounds were rather faint, but there was no murmur. His pulse was 80 and regular. The systolic pressure was 120 millimetres. The urine was free from albumin. Three days later he complained of epigastric pain and tightness across the chest. He said that he could feel 'something jumping about inside.' The frequency of the radial pulse was now only 20, while the frequency of the venous pulse in the neck, which was very marked, was 80. A soft systolic murmur could now be heard at each contraction of the ventricles. On the X-ray screen thirty-two auricular contractions could be counted to nine ventricular. The dissociation of rhythm was clearly visible. Strychnine and caffein were given and the normal rhythm soon returned. Two days later the drugs were discontinued; within fourteen hours he had another attack. 'Everything in the room was turning round,' he said, and he was evidently in great distress. The pulse at the wrist fell to 16, while the venous pulse was 90. He was given strychnine subcutaneously, and caffein by the mouth. Again he rapidly improved.

Under treatment the attacks diminished in frequency, though in one the pulse fell to 12. After about three weeks' immunity he had a series of severe attacks, being unconscious during the periods of bradycardia, and regaining consciousness as the pulse revived. He then passed into an epileptiform state, in which he bit his tongue and lost control over the sphincters, while the legs and back were quite rigid. For about three days he passed through these phases in turn: the ventricles stopped and he became unconscious; the pulse returned, he became convulsed or excited. On several occasions competent observers believed him to be dead, yet on powerful stimulation the heart could be made to beat again, and he came back to life for a time. At last it stopped for ever.

The heart was found to be only slightly hypertrophied, and there was a little atheroma of the coronary arteries. No other signs of disease could be found until the muscular tissues near the auriculo-ventricular bundle were examined microscopically in serial sections, when degenerated fibres were found embedded in a mass of fibrous tissue.

There had evidently been a progressive fibrosis involving the bundle of His, so that a partial heart-block ultimately became complete. At first drugs which improve conductivity appeared to combat this, but as the strand of connecting tissue became narrower they failed. Even in complete heart-block the ventricles may continue to beat slowly and independently, for they have a rhythmical power of their

own. This, however, is usually not adequate to maintain the circulation efficiently.

As a large proportion of cases of heart-block are due to syphilis, Wassermann's reaction should be tried in every case, and if it is positive, vigorous anti-syphilitic treatment must be carried out, for, though often disappointing, it affords the best chance of relief. In young people with a history or symptoms of rheumatism effective doses of sodium salicylate should be given, for there is no commoner cause of heart-failure in the young than rheumatic carditis. Atropin is indicated on theoretical grounds, as it paralyzes the inhibitory action of the vagus, but it does not appear to give good results when the block is complete. Caffein and strychnine are worth trying during the paroxysm. They both appear to improve conductivity, and the former diminishes the action of the vagus on the heart as well. Theobromine may suit the cases with high blood-pressure better than caffein. Digitalis is often said to be contra-indicated as long as the block is incomplete, since it depresses the conductivity of the bundle. But, as Lea and others have pointed out, when the block has become complete, digitalis cannot depress conductivity any farther, while it may improve the contractions of the independently acting ventricle. And there may be an actual advantage in converting an incomplete into a complete heart-block so as to cut off disturbing influences from the auricle.

5. **Pulsus Alternans.**—*A regular succession of small and large beats.* Whereas deficient conductivity will

lead to heart-block, impaired contractility will lead to pulsus alternans. The latter is generally attributed to variation in the number of the ventricular fibres which contract during systole. But if this were so, there should be cardiographic evidence of its existence which is not forthcoming. Another view is that the heart, as a whole, is defective in contractile power. This rather contradicts the 'all for nothing' principle of cardiac contraction. Pulsus alternans is usually associated with high blood-pressure. It may be brought out only on exertion, and it is well to try the effect of exercise in suspected cases. It is difficult to recognize the condition by the finger even when the pulse tracing shows obvious alternation. As the systolic pressure of the larger beats is higher than that of the small beats, the condition may be recognized by applying the sphygmomanometer and just raising the pressure in the armlet sufficiently to halve the pulse-rate at the wrist. This alternation implies a grave condition, for it is the expression of an exhausted heart, with great impairment of its reserve force. In Lewis's graphic phrase, 'it is the faint cry of an anguished and fast failing muscle, which, when it comes, all should strain to hear, for it is not long repeated.' According to Davenport Windle, the practical value of recognizing this altered rhythm is that it occurs in aged people before the symptoms of heart failure. Thus it is a danger signal. He states that in any patient with arterial disease and alternating pulse the occurrence of angina may be confidently

predicted, unless dropsy sets in, when angina, if previously present, ceases as a rule.

Apart from angina, the dominant symptom is apparently causeless breathlessness. If this occurs in an elderly patient with high pressure, but in whom the heart is only a little enlarged and free from valvular defects, the lungs clear and the kidneys not evidently diseased, the presence of alternating pulse is probable. The dyspnœa is sometimes paroxysmal, or there may be Cheyne-Stokes respiration. The gravity of pulsus alternans may be gathered from the fact that in Windle's series of seventeen cases no patient lived longer than seventeen months after he first observed pulsus alternans. Its diagnosis from the bigeminal pulse of ventricular extra-systoles is important, for the latter means no more than increased excitability of the heart; and although it may be associated with cardio-sclerosis, it is in no sense an index of the degree of myocardial degeneration, and does not afford any indication as to the expectation of life. The distinguishing point is that in extra-systole the long pause follows the small beat, while with an alternating pulse the intervals may be equal, or if unequal the shorter pause follows the smaller beat. On auscultation the characteristic rhythm of the extra-systole will be recognized. It may be expressed thus: 'Lub—dup tu tup,' followed by a long pause.

Conclusions.—Though much remains to be worked out, we have already learned much as to the widely different significance of the various types of irregularity.

Sinus irregularity has no real significance. Extrasystoles, produced either in the auricle or ventricle, mean increased irritability of the heart, but not necessarily any serious organic defect, and are compatible with many years of active life. Auricular fibrillation means a serious mechanical defect, which is an important factor in inducing heart-failure. Heart-block, except when due to a temporary toxic cause, is always grave. Alternating pulse is prognostic of death within two years. The recognition of the first two types in young persons should prevent us in the future from alarming a patient, already nervous, by the vague but terrifying diagnosis of weak heart. Sinus irregularity will probably subside after adolescence. This explains those cases in which patients say that they have had a 'weak heart' for years, and nothing can be found on examination.

Treatment.—In the light of the new evidence as to cardiac rhythm, the action of drugs ordinarily used for diseases of the heart has had to be reinvestigated. The data are still insufficient, but some conclusions have been arrived at.

Digitalis is by far the most potent of these drugs, but it is a two-edged sword, and very unsatisfactory results may follow its use in unsuitable cases. In animals, besides its action on the heart, it has a pronounced effect upon the bloodvessels, causing vasoconstriction, and therefore a rise of blood-pressure. Recent observers have failed to find this vaso-constrictor action in human beings. Still, it does not seem

to give such satisfactory results when the pressure is high and, indeed, Withering, when he introduced the drug, did not advise its use in the type of case which we now know has a raised pressure. In such circumstances I usually prefer strophanthus.

Turning from the vessels to the heart, we have to distinguish between the action of the drug on conductivity, on tonicity, and on contractility. On *conductivity* digitalis often has a depressing effect; Mackenzie has shown that it causes a delay, and sometimes a stoppage, in the transmission of the impulse from auricle to ventricle. Conduction is such an important function of the auriculo-ventricular bundle that, when this structure is involved, as in partial heart-block, digitalis is contra-indicated. In many cases of heart-block the systolic pressure may be quite high, although the arterial pulse is so slow. Gibson has seen three cases in which it ranged from 210 to 270 millimetres. In one such case, where the radial pulse was 32, while the venous pulse was 64, I found that the systolic pressure was more than 300 millimetres. The diastolic pressure, however, is relatively low.

On the other hand, when auricular fibrillation is found in mitral stenosis, digitalis is a most useful drug. Here the bundle itself is not at fault, but lowering its conductivity enables it to ignore many of the irregular stimuli reaching it from the auricle. The most striking and immediate benefit I have ever seen from digitalis was in a case of mitral stenosis with auricular fibrilla-

tion. Mackenzie believes that the drug owes its reputation to its remarkable action in these cases. But digitalis also has a great effect on *tonicity*. Cushing says, 'In cases of dilatation with weak and insufficient systole, its action is almost specific. This is true, whether one or both ventricular chambers are affected, so long as the cardiac muscle has not undergone degeneration.' In the acute dilatation of febrile affections, however, it has no effect, and not much on the dilatation secondary to cardio-sclerosis. Coupled beats are a sign to stop the drug for a time.

On *rate* it has very little action, except where rapidity is due to dilatation. On *contractility* it occasionally has a depressing effect.

We may classify the reaction of the different types of irregularity to digitalis in tabular form as follows:

Digitalis is indicated in	Digitalis is of no use in	Digitalis is contra-indicated in
Auricular fibrillation. May be indicated in Heart-block.	Sinus irregularity. Ventricular extra-systoles. Paroxysmal tachycardia. Toxic myocarditis.	Pulsus alternans.

Strophanthus is not so readily absorbed as digitalis, but intravenous injections of strophanthin produce a very powerful effect. A dose of $\frac{1}{500}$ to $\frac{1}{250}$ grain may be given in a little saline, and repeated in two hours,

and then in four hours. If digitalis has been recently given it has been considered dangerous to give intravenous strophanthin, but this has not been my experience.

The action of the caffein group and of strychnine has already been considered under heart-block, while quinidine has been discussed under auricular fibrillation.

This is not the place to attempt to deal with the treatment of cardiac arrhythmia in genoral; my object is simply to call attention to certain modifications in our ideas which result from our fresh knowledge of the functions of the cardiac muscle.

The Effort Syndrome.

It has long been recognized that certain heart symptoms are common in warfare, and they were carefully studied by Lewis in the late war. His conclusions being based on physiological method are appropriate to our present topic. The importance of the subject can be realized from the fact that cardio-vascular symptoms are second among medical ailments as a cause of invaliding out of the Army, amounting to 10 per cent. of all cases, both medical and surgical. No less than 70,000 soldiers reported sick on such grounds, only about 10 per cent. of these being cases of structural heart disease; of the remainder the vast majority were, in military parlance, 'Disordered Action of the Heart.'

In a healthy man, during or after sufficiently strenuous exercise, certain symptoms and certain physical signs are presented. He becomes breathless and conscious of the heart's action, while giddiness, faintness, and fatigue may ensue. Later there may be tremors, stiffness of the muscles, and exhaustion. With extreme effort precordial pain may be produced. During the exercises the rate of the heart and the blood-pressure are raised, while the accessory muscles of respiration are brought into action. Now, these are precisely the symptoms called disordered action of the heart (D.A.H.) in the Army. The difference is that they are produced by an unduly small amount of exertion, and persist unduly after that exertion. The degree of effort needed to call them forth is an inverse measure of morbidity. It is because the signs and symptoms are largely—in some cases wholly—the exaggerated physiological responses to exercise that Lewis terms the condition the 'effort syndrome.'

The largest number of the patients form a group showing signs of constitutional weakness, nervous or physical or both. Another large group are those worn out by exposure, exertion, lack of sleep, and the continuous strain of front-line work. A third important group occurs among those convalescent from acute illness.

Another group are those suffering from infections, such as incipient tuberculosis, local collections of pus, and infections of the intestinal tract. Small

groups are those showing either delayed recovery from gas poisoning, or incipient but unrecognized heart disease.

The strain of war imposes entirely fresh conditions, under which some break down quickly, others only after it has been severe or prolonged. War is 'a test which emphasizes a recognized defect; it confirms a suspected or discovers an unsuspected weakness; that is its general method. But often it sifts unfairly, submitting its victims to wholly unnatural strains and accidents.' The apparent frequency of the syndrome in soldiers is chiefly, if not entirely, due to its unveiling by circumstances which the civilian does not meet. The conclusions worked out on the large scale under military conditions are applicable to similar cases occurring in civil life and are, therefore, of permanent value. It is not surprising to find that the greater number of the cases were recruited from sedentary or light occupations, because many had tended to drift into such occupations as appropriate to their strength, and because the following of a sedentary calling tends to decrease physical fitness. Alcohol can be exonerated as a cause; nor does tobacco seem to increase the liability to the condition though it aggravates it once it has been produced. Lewis does not regard hyperthyroidism, gas-poisoning, or shell shock, as any more than aggravating causes.

There is little doubt that in the earlier days of the war many of these cases were treated on mistaken

lines. The very labelling of such cases as suffering from some form of heart disease is not only inaccurate, but also injurious to the sufferer. Keeping them in bed also does harm rather than good, while drugs are of little avail. The most successful plan has been that of graded exercises. Preliminary examination will eliminate cases of mitral stenosis, aortic disease, aneurism, or material cardiac enlargement, as well as cases suffering from manifest diseases of other systems; these should be recommended for discharge as permanently unfit. With the remainder drills or games should be so graded that no man is submitted to stiff exercises before his tolerance of easier exercises is thoroughly established. The drills in the case of soldiers should consist, so far as possible, of exercises familiar to them in the Army so as to avoid loss of time in acquiring a knowledge of them. It is advisable to break the monotony of longer drills by short set games. In this way the average stay in hospital can be reduced to six to ten weeks. Half of them may be rendered fit for full or light duty, while the other half have to remain in the stationary class or be discharged as unfit. It is interesting to note that 10 per cent. of the total were able again to acquit themselves in the firing-line, but that in those who had to be discharged improvement was no more than slight even nine months later.

Compensation.

Certain physiological principles will help to a comprehension both of the occurrence and of the failure of compensation.

If the cardiac muscle be exposed to an increase of its load, such as occurs when there is a greater resistance to the outflow of blood, it responds by increased energy of contraction. With each addition to its load there is more shortening of the fibres. Of course, there is a limit to this, and, if the load be increased too much, the muscle may fail to respond at all. It has been said that the heart's motto is 'All or nothing': the tendency of the cardiac muscle is to rise to an emergency and do all that is required of it, but, if it be unable to meet the demands in full, to do nothing at all. In this we see the explanation both of compensation and of syncope; the muscle goes on responding until the proverbial last straw proves too much for it.

How great is this reserve force of the heart is seen by the experiment in which a ligature is placed round the pulmonary artery and slowly tightened. The lumen of the artery may be reduced to one-third of its normal size without perceptibly diminishing the output of blood, though the intracardiac pressure will have to rise three- or four-fold. The same thing is observed if the work of the heart be augmented by increasing the diastolic inflow, either by pressure on

the veins of the abdomen, or by injection of large quantities of fluid into the circulation, or by damaging the aortic valves. Within very wide limits, the output of the heart is independent of the resistance (Starling).

Recent work has yielded an interesting explanation of this. A. V. Hill proved that the energy set free from a muscle varied with its initial length. In other words, the strongest stimulus to a muscular contraction is the previous stretching to which it has been subjected. Starling applied this principle to the heart and showed that an increased peripheral resistance caused the heart to dilate until diastolic stretching developed sufficient energy to enable the heart to put out an amount of blood equal to that entering it. A new point of equilibrium is reached, so that dilatation in its inception is compensatory. Now, a physiological dilatation of this sort should be temporary, but if the maximum elongation obtainable is not enough to develop sufficient energy, the heart must remain dilated. This is unlikely to occur if the nutrition of the muscle is unimpaired. The reserve force of the normal heart is enormous. But if the muscle is diseased its contractility is diminished.

It is often a surprise to find a high blood-pressure in association with a failing heart and a feeble pulse. It is not that the heart is failing behind the high pressure, for lowering the pressure does not relieve the heart. Nor can it be that as the output of the heart

falls, vaso-constriction occurs to diminish the size of the bed to be filled, for this would only account for pressure being maintained at its normal level. The rise of pressure is an attempt to stimulate the heart to renewed effort by stretching its muscle, an attempt which, in this case, is unsuccessful, as the myocardium cannot respond.

In the same way a rise of venous pressure causes the blood entering the heart to stretch the auricle more thoroughly and stimulate it to a better beat. The short, sharp auricular contraction suddenly squirting blood into the ventricle is the best possible stimulus to it. But this rise of venous pressure has drawbacks: it tells directly on the thin-walled capillaries, unlike raised arterial pressure, which is shut off from the capillaries by the constriction of the arterioles. Their thin walls allow transudation of fluid to occur into the surrounding tissues: hence congested liver, albuminuria, and dropsy.

For continued additional work to be performed, hypertrophy of the cardiac muscle must occur. One result of the activity of the muscle must be an additional lymph flow, and increased nutrition would lead to increased growth of the cells, which, no doubt, is the chief way in which hypertrophy is brought about.

When adequate hypertrophy has produced complete compensation, it may be asked, In what respect is the hypertrophied heart inferior to an ordinary one? It

is as powerful, and it can meet the demands made upon it. It is, however, working much nearer to the limits of its power, so that it has much less reserve force, and its capacity for adjusting itself to unusual calls upon it is therefore restricted. It is, in fact, a spendthrift heart, while a dilated heart is a bankrupt one.

The newer work explains why the heart, though it can adjust itself so well to increased resistance to its systolic output, is very intolerant of interference with its diastolic filling. One important factor in this filling is the aspiration of blood into the chest by the respiratory movements. When persons are crushed to death in a crowd they die of syncope, not of asphyxia. Yet it is the compression of the thorax that kills, and children, with their comparatively yielding chests, suffer first. They die because the heart cannot be properly filled. Again, rupture of an aneurism of the first part of the aorta into the pericardial sac may be immediately fatal, though only 8 to 10 ounces of blood are extravasated in some cases. No one dies from such a small loss of blood as that; death is not from hæmorrhage, but from the sudden rise of intrapericardial pressure, which prevents the diastolic filling of the heart. In pericardial effusion the accumulation of fluid is not so rapid, so that the heart has time to accommodate itself to some extent; but here, too, its action is seriously embarrassed. Interference with the diastolic filling strikes at the very origin of the rhythm by depriving the heart walls of that stretching which is so powerful a stimulus to contraction.

CHAPTER XIII

THE VASOMOTOR SYSTEM IN DISEASE

The introduction of precise methods of registering blood-pressure in clinical work has naturally directed much more attention to the part played by the vasomotor system in disease.

Briefly, the functions of the vasomotor system are two—to regulate the general blood-pressure, and to regulate the local blood-supply. These functions are carried out by the following structures:

1. **The Vasomotor Centre,** beginning 1 or 2 millimetres below the corpora quadrigemina, and ending 4 millimetres above the calamus scriptorius. But there must also be secondary centres in the cord, since asphyxia can still produce a rise of blood-pressure after the medullary centre has been cut off, though not after the spinal cord has been destroyed. There is, further, some degree of local vasomotor control, since some recovery of tone may occur after complete separation of the vascular area from the central nervous system. This is probably due to the usual effect of stretching plain muscle—namely, that it contracts more forcibly.

2. **Efferent Nerves,** which can either constrict or dilate the vessels.

(*a*) *Constrictors.* — These are much the most numerous, and are confined to the sympathetic. Leaving the spinal cord in the anterior roots of the second thoracic to the second lumbar nerves, they pass into the sympathetic chain by the white rami communicantes, and end around a nerve cell in the first ganglion they reach. Here a new non-medullated 'postganglionic' fibre starts, which is distributed to its appropriate destination. This is the method of distribution, whatever the part of the body to be supplied.

(*b*) *Dilators.*—These are not nearly so numerous. The muscular coats of the bloodvessels being always partly contracted, it is possible for dilatation to be produced by inhibition of a constrictor. Pure dilator nerves will, therefore, only be found where there is a special need for marked and rapid dilatation. Thus the chorda tympani nerve carries dilator fibres to the submaxillary gland, and the auriculo-temporal nerve to the parotid. The nervi erigentes form part of the pelvic visceral nerve springing from the second and third sacral roots. All these belong to the *parasympathetic* system—*i.e.*, those fibres with visceral functions which leave the central nervous system above the cervical or below the lumbar plexus. Unlike the constrictors, they have their ganglionic station close to their destination.

The existence of dilator fibres, also, in mixed nerve

trunks has been proved by taking advantage of the fact that constrictors degenerate more quickly after section, and are more readily affected by cooling than dilators; on using slow, rhythmically repeated shocks (one per second) a dilator effect can be obtained, whereas rapidly interrupted shocks would excite the constrictors.

Dilator nerves to the limbs have appeared in a new aspect, however, since Bayliss has shown that they seem to be in every way identical with the sensory nerves. Under experimental conditions, at any rate, these fibres are able to carry 'antidromic' impulses—that is to say, the same fibre is able to convey sensory impulses towards the brain and dilator impulses towards the periphery. This is a disturbing fact, because opposed to our fundamental conceptions of the functions of the anterior and posterior roots, but it cannot be neglected on that account. The missing link in the evidence at present is the way in which these fibres are connected to the muscular coats of the vessels.

8. **Afferent Nerves.**—Impulses may pass to the vasomotor centre calling for a general rise or fall of blood-pressure. While the efferent nerves may produce either a local or a general effect, the afferent can only produce the latter. They are of two kinds:

(*a*) *Pressor*, producing a rise of blood-pressure. All sensory nerves are pressor in their action, causing the vasomotor centre to throw out increased constrictor impulses, particularly to the splanchnic area.

This explains the rise of pressure which may be seen in all painful conditions. It has the effect of increasing the blood-supply to the brain; at the same time vaso-dilatation occurs at the site of the painful stimulus through the antidromic fibres. In this way the blood-supply is simultaneously increased at the point where the painful stimulus is *received* and where it is *perceived*, thus facilitating the appropriate reaction in each case.

(*b*) *Depressor*, producing a fall of blood-pressure by causing the vasomotor centre to relax the normal constrictor tone in the splanchnic area, which thereby becomes flushed with blood. The only pure depressor nerve is the depressor branch of the vagus. This may be regarded as a way of escape for the heart, if it be labouring against too high a blood-pressure.

The existence of depressor fibres in sensory nerves may also be demonstrated, since on regeneration after section they recover before the pressors, and on cooling they retain their function longer. Stimulation of the mucous membrane of the rectum and vagina may also produce a depressor effect, especially under light anæsthesia.

Failure of the vasomotor system to respond adequately to the needs of the body may result either in insufficient regulation of the general blood-pressure or of the local blood-supply. We will take examples of each.

It is not uncommon to be told by a patient that one of his first symptoms was that, on getting out of bed

in the morning to pass water, he fainted. Normally a change of posture should not produce a perceptible effect on the blood-pressure, the slightest degree of cerebral anæmia at once inducing the vasomotor centre to throw out increased constrictor impulses, which, by tightening up the splanchnic bloodvessels, forces more blood to the head again. In this way the effect of gravity is counterbalanced. But if the vasomotor response is inadequate, the erect posture will lead to cerebral anæmia, and hence to fainting. If the intra-abdominal pressure is lowered at the same time by the emptying of the bladder, this is still more likely to happen. Fainting following the tapping of ascites is due to the same cause, and, as is well known, it may be prevented by tightening up a binder round the abdomen as the fluid escapes, thus avoiding splanchnic engorgement.

During prolonged recumbency the vasomotor centre will lose its promptitude in responding to changes of posture, which explains the faintness that any patient is liable to on first getting out of bed after a long illness.

Insomnia may be due to inadequate control of the general blood-pressure by the vasomotor system. Ordinarily a certain degree of cerebral anæmia plays an important part in inducing sleep. The hypnotic effect of taking some warm fluid or a little food is due to the vaso-dilation it induces in the splanchnic area, thus drawing away blood from the head. Cold feet may help in causing insomnia by keeping too much blood at the opposite end of the body.

Insomnia is often troublesome in conditions of high arterial tension. Apart from measures directed towards the cause of the high tension, we should treat this symptom by propping the head up on fairly high pillows, by flushing the abdominal vessels by a drink of hot water, and by preventing the feet from getting cold.

In 'functional' or orthostatic albuminuria, inadequate vasomotor control, as we have seen, plays an important part. The circulation through the kidney is in consequence retarded by back pressure in the erect posture. Albumen, therefore, is present in the urine secreted in the day, but absent from that secreted while in bed.

Examples of failure in the regulation of the local blood-supply are seen in Raynaud's disease and in erythromelalgia.

At first sight it is not a little surprising that the organs composing the 'tripod of life'—the brain, the lungs, and the heart—either lack or are very scantily supplied by vasomotor nerves. Yet on consideration it will be clear that it is just because they are so important that they cannot be subservient. For we must remember that the vasomotor system can override the local needs for the general demands. The efferent path in a reflex arc is open to impulses coming from many quarters, although the afferent channel is reserved for impulses coming from the particular organ it supplies.

The organs composing the tripod of life cannot allow their local needs to be subordinated in this

way. This may cause them in disease to over-ride the interests of the general economy for their own advantage; though it is merely an example of the survival of the fittest, the most vital organs being protected at all costs.

It is for just such reasons that we find the spleen, a comparatively leisured organ, has its blood-supply most subordinated to the vasomotor system. The splanchnic area plays the largest part in vasomotor effects. Now, it may well be that the stomach or intestines cannot spare their extra blood at a time when vaso-constriction is called for in the general interests of the economy. The spleen is a portal reservoir which will not suffer vitally from a vaso-constriction, and so it is called upon. It is because of its great liability to passive change and of its sub-ordination to the general interests that diseases of the spleen are accompanied by so few definite physio-logical features. As Frederick Taylor tersely put it, the spleen is more sinned against than sinning.

The way in which the local needs may be over-ridden by the vasomotor system is seen in the blanched condition of the skin in the cold stage of fever, and in the dyspepsia that may be produced by severe mental effort during active digestion through blood being forced into the head from the abdominal vessels, which are thus rendered too anæmic.

We may consider some of the results of the exemp-tion of the 'tripod' of brain, lungs, and heart from the operation of this action of the vasomotor system.

Brain.—Munro, in 1783, enunciated the dictum that the quantity of blood in the cranium is a constant, since the brain substance is incompressible and enclosed in a rigid box. Allowing for variations in the quantity of cerebro-spinal fluid, this is true.

The first effect of a rise of arterial pressure will be to express the cerebro-spinal fluid from the cranium, and then to compress the cerebral sinuses until the pressure in them rises to that which the brain substance exerts against them. Thus the conditions approximate to those obtaining in a system of rigid tubes.

Now, the one part of the brain that must keep up its supply of arterial blood is the medulla, for here are the centres that are essential to life. If the blood supplied be too rich in carbon dioxide, the respiratory centre is excited to increase the respiratory rhythm; if the quantity of blood be not adequate, the vaso-motor centre is excited by the slightest degree of cerebral anæmia to contract the vessels in the great splanchnic pool, and thus force more blood up to the head. There are two ways in which the blood-supply to a part may be increased—local vaso-dilatation, or vaso-constriction elsewhere. In a rigid box a local relaxation of muscular tone would not be very effective, for it might be overriden easily by the intracranial pressure already existing. To force the blood in by a general rise of blood-pressure is to employ a much more powerful mechanism. Thus it is we find that the blood-supply to the brain is mainly

controlled by means of the splanchnic area, which, in its turn, is controlled by the vasomotor centre within the cranium.

This does not mean that there are no vasomotor nerves in the cerebral vessels—such have been found by Morison and by Gulland—and perfusion of adrenalin will cause a slight contraction of these vessels. But it is safe to assert that they must play an entirely subsidiary part, and that all the vasomotor effects ordinarily observed can be adequately explained without reference to them.

To avoid cerebral anæmia, the general blood-pressure must be kept at a point above the intracranial pressure. This was clearly proved by Cushing, who adopted the method of varying the intracranial pressure by introducing normal saline solution into the cranial cavity from a pressure-bottle.

The effect on the general blood-pressure was observed by means of a tracing taken from the femoral artery. Until the intracranial pressure exceeded the blood-pressure, nothing more than a slight quickening of pulse and respiration occurred, and even this could be avoided if the fluid did not interfere with the sensitive dura. But when that point was reached, the blood-pressure was at once raised until it was again greater than the intracranial pressure. This was repeated with each increase of intracranial pressure until the blood-pressure was forced to a level considerably over 200 millimetres of mercury. Then the vasomotor centre began to show

signs of giving way. The splanchnic vessels could be seen to contract every time the brain was compressed, and to dilate again as the pressure fell. If the pressure were raised too rapidly, the so-called major symptoms of compression might be produced—convulsions, evacuation of the bladder and rectum, cessation of the respiration and pronounced vagus effect upon the heart, often causing its complete arrest for from ten to twenty seconds. Then followed a release from this extreme vagus inhibition, and the vasomotor centre began to exert its striking influence. If the vagi were divided before the compression was applied, the blood-pressure could be seen to correspond even more closely than before to the degree of intracranial tension, always remaining slightly higher. If both vagi and spinal cord were thus divided, an increase in intracranial tension did not affect the level of the blood-pressure in the slightest degree, showing that the adjustment is brought about by constriction of the bloodvessels in the rest of the body.

The clinical importance of this in the treatment of cerebral hæmorrhage has been brought out by Leonard Williams.* 'If we reduce blood-pressure—*e.g.*, by venesection or amyl nitrite—to the point at which the reduction will be effective in checking the hæmorrhage, we are obviously in danger of reducing it to the point at which the medulla is starved. There may be a margin of safety—a point to which you

* *The Hospital*, December 14, 1907.

may reduce the blood-pressure so as to moderate the hæmorrhage, without seriously diminishing the supplies to the medulla—but surely this is a razor's edge on which no practical physician will voluntarily choose to tread. The manometer has no information to give us on this crucial point. It tells us, no doubt, that the arterial pressure is very high, but we know that the arterial pressure was high before the accident, and that it is now higher still, because it has to overcome an augmented intracranial pressure; but the instrument does not, and cannot, tell us whether we ought to bleed the patient at all, and, if so, what are the danger-signals. For there are no danger-signals. When the arterial pressure is reduced below the intracranial, death is instantaneous. That venesection may be resorted to in apoplexy not only with impunity, but with conspicuous benefit, is a fact which must be accepted on the testimony of very competent physicians; that it is at best a dangerous expedient, dangerous to the life of the patient and extremely dangerous to the reputation of the practitioner, the above considerations are surely sufficient to show.'

The absolute necessity of maintaining the blood-pressure at a higher level than the intracranial establishes a vicious circle, for the hæmorrhage produces a rise of pressure, and the rise of pressure increases the hæmorrhage. A rising blood-pressure in cerebral hæmorrhage is of very grave prognosis, as it shows the bleeding is still continuing.

Is there any way of lowering intracranial pressure directly? Then the vasomotor centre would allow the blood-pressure to fall; this would assist the arrest of hæmorrhage, and the vicious circle would be broken. Lumbar puncture will diminish intracranial tension, and has, therefore, been recommended in such cases. It has been thought to be risky, in that it will leave the arteries less supported, and therefore more liable to bleed. But as soon as the intracranial pressure is reduced the blood-pressure will fall, and therefore the liability to hæmorrhage is diminished, though, one must admit, not abolished. That the blood-pressure can be reduced in this way I have had the opportunity of observing. A man in whom I had diagnosed cerebral hæmorrhage had a blood-pressure rising from 165 to 210 millimetres. Lumbar puncture withdrew blood-stained cerebro-spinal fluid. The pressure fell at once to 175, and then more gradually to 135 millimetres, while consciousness was soon regained.

Cushing's experiments also explain why we so frequently find more than one hæmorrhage into the brain substance, if the initial one be at all large. If looked for, small hæmorrhages into the pons will be found very commonly in cases of ordinary lenticulo-striate hæmorrhage. It was formerly a puzzle to decide how these were produced, and whether they occurred simultaneously with, before, or after the large hæmorrhage. It is now clear that the large hæmorrhage is responsible for driving up the general blood-pressure so much that diseased arteries in

other parts of the brain are unable to withstand the strain.

Lungs.—The absence of direct vasomotor effects in the pulmonary vessels has some interesting bearings on the treatment of hæmoptysis, which have already been touched upon in the first chapter. It must be remembered, however, that the lung receives blood by another channel also, the bronchial arteries, springing from the aorta. In the hæmoptysis of mitral stenosis the pulmonary vessels alone are involved; adrenalin and other constrictors will therefore do harm by forcing blood from the systemic into the pulmonary vessels. But amyl nitrite will do good, because it will relieve the engorged lung by dilating the systemic vessels. In the hæmoptysis of phthisis, either pulmonary or bronchial vessels may be eroded, though the former are more likely to be implicated, since they are more numerous. But styptic drugs would be inadvisable even if we could be sure that a bronchial artery were the source of the hæmorrhage, for any benefit derived from their local action would be outweighed by the general rise of pressure and by the pulmonary turgescence, which might cause other weak spots to rupture. Nitrite of amyl would still be useful, as the widespread dilatation would draw blood away from the lungs, and thus more than counterbalance the risks of reopening the bleeding-point. Also the lowered pressure would favour the sealing of this point by blood-clot. The same principles would therefore guide us, whichever set of vessels were involved.

Œdema of the Lungs is a common terminal event. In Cohnheim's phrase, a man does not die because he gets œdema of the lung: he gets œdema of the lung because he is dying. It is held to indicate a somewhat rapid failure of the left ventricle, while the right ventricle continues to beat forcibly. As there is no vaso-constrictor action in the pulmonary vessels, there is nothing to prevent engorgement of the lung capillaries, and an effusion must occur into the alveoli. Leonard Williams* has called attention to an acute form of this œdema, and from the correspondence which followed his communication it is clear that the condition is not uncommon, though very inadequately recognized in this country.

A patient usually with high blood-pressure and often with aortic disease is seized, generally while recumbent, with sudden dyspnœa and cyanosis. He becomes greatly distressed, throwing himself about or coughing incessantly. Then a quantity of froth, which has been compared to that of beer, only finer and thinner, and often blood-stained, begins to issue continuously from nose and mouth. Death may occur within a few minutes, and will not be delayed beyond a few hours, if the condition cannot be relieved.

As the heart continues to beat strongly after the patient is apparently suffocated, it might be urged that death could not be from syncope. But it seems likely that the forcible sounds are produced by the

* *Lancet*, December 7, 1907.

right heart. The most probable sequence of events is this: The left heart is already loaded to its full capacity; the proverbial last straw is too much for it, and it breaks down, while the right heart goes on beating still, forcing blood into the lungs until they become engorged, since they are unable to shut off any of the blood-supply by vaso-constriction. An outpouring of serum occurs into the alveoli in such quantities that the patient is drowned in his own secretion. Two facts support this view: the commonest cardiac lesion in these cases is aortic regurgitation, which is known to terminate not infrequently in sudden stoppage of the heart; and venesection (10 to 12 ounces), according to French authorities, is the only effective treatment, and this would relieve the overloaded right heart and the stagnant pulmonary circulation.

Heart.—It is not difficult to understand the absence of vaso-constrictors to the coronary arteries. If a rise of general blood-pressure is produced by vaso-constriction, the heart is given more work to do, so that a better blood-supply must be given to its muscle. If vaso-constriction took place in the coronaries, their blood-supply would be diminished, but in its absence the rise of pressure automatically forces more blood into them. If the heart has less work to do, the pressure falls and the coronaries receive less blood. In this way the supply to the heart muscle is made proportional to its requirements. The power of compensation is extraordinary so long as the coronary arteries remain supple, but if

they become atheromatous, this means of regulation is frustrated, and compensation breaks down.

The heart's ties with the vasomotor system are most intimate on the afferent side through the 'private path' of the depressor nerve. Through this the heart can always produce a fall of pressure should it find itself embarrassed by a pressure that is too high for it. It might be thought that under these conditions an abnormally high pressure could never be maintained. But so long as the heart can meet the high pressure, there is no inducement for it to call the depressor nerve to its aid. We may safely assume, however, that when the pressure is kept up at a point at which the heart begins to dilate, a structural change must have occurred in the walls of the visceral vessels which renders them incapable of relaxing in answer to the appeals of the depressor nerve.

On Blood-Pressure.

The vasomotor system is, of course, only one factor in determining the blood-pressure. Its importance lies in its sensitiveness to the needs of the organism; like all nervous mechanisms, it is characterized by the rapidity of its reactions.

The pressure, by which the whole of the vascular system is kept distended with blood, is the product of—

1. The beat of the heart.
2. The peripheral resistance.
3. The elasticity of the vessel wall.
4. The volume of the blood.

1. **The Beat of the Heart.**—While the energy of the heart necessarily originates the pressure in the vessels, an increase in its output will cause a rise in pressure only so long as the size of the arterioles remains the same. When there is a large amount of blood in the great veins awaiting entrance into the heart, this stretches the right side of the heart, reflexly causing acceleration of the rate, but not a rise of pressure. Indeed, the nervous mechanisms provide that the pulse-rate will vary almost inversely with the blood-pressure. If the pressure rises to a point at which the cardio-inhibitory centre in the medulla is stimulated, the heart is slowed through the vagus, so that unnecessary work is avoided.

2. **The Effective Peripheral Resistance** is provided mainly by the constriction of the muscular coats of the small arteries, which are chiefly controlled by the vasomotor nerves. That the capillaries can change their calibre under the influence of chemical stimuli is, however, now proven, and the arterioles themselves are not unresponsive to such. Thus Gaskell showed that the acid products of metabolism would dilate the peripheral vessels, and thus provide for their own removal. In the first stage of high blood-pressure in disease there need be no structural change in the vessel wall, but the muscular coat contracts, presumably under the influence of toxic agents. This is in accordance with the general principle that the important functions are subserved by both a chemical and a nervous mechanism. How essential the nervous

factor is in maintaining the pressure is seen on destruction of the cord, when the vessels lose their tone so completely that the circulation cannot proceed. It is the splanchnic area which has in this way by far the greatest influence on the general blood-pressure.

3 **The Elasticity of the Vessel Wall** tends to equalization of the pressure in systole and diastole. For, as the vessel distends with each heart-beat, the pressure becomes lower, and as it retracts during diastole, the pressure remains higher than it otherwise would do. With loss of elasticity comes a more violent fluctuation. Mark the tendency to a vicious circle. Continued high pressure diminishes elasticity, thus increasing the work of the heart. The heart has to hypertrophy, and each beat produces a still higher systolic pressure in a tube that is becoming more rigid. The sequel must be that either the vessel gives way, or else the heart dilates behind the strain.

Another consequence, as shown by A. V. Hill, is that the velocity of the pulse-wave is greatly increased in rigid arteries. This is, of course, quite distinct from the frequency of the pulse.

4. **The Volume of the Circulating Blood** has within wide limits in the normal animal only a subordinate and temporary influence on mean blood-pressure (Janeway). Its variatiens can be easily compensated for by the vasomotor system. This limits the useful-

ness of venesection to those cases where the compensating mechanism has become damaged. Thus, if the right auricle is becoming so dilated that the transmission of the wave of contraction to the ventricle is a matter of difficulty, venesection may permit it to regain its tone; or if the responsiveness of the vasomotor system is becoming dulled by arterio-sclerosis or toxic agents, reduction of the volume of the blood by bleeding can diminish tension.

The blood-pressure in health reflects the various physical and mental states; a cold bath, a meal, the smoking of a cigar, an animated discussion, all affect it. Irrespective of such disturbances, there are also small diurnal variations. It might be questioned whether this does not destroy the value of a blood-pressure record. But no one questions the value of a temperature chart which also shows fluctuations not produced by disease. And no one doubts the importance of a pulse record, although nervousness affects the pulse far more than the pressure. The alterations of pressure in disease far exceed these minor changes. It is of course necessary to make the observations under similar conditions and at the same time of day.

The clinical value of observations on the blood-pressure is doubted only by those who have never made them. Unlike many another apparatus, there is no sign of the sphygmomanometer being abandoned by those who have once used it systematically; they only change the form of apparatus as mechanical improvements are made. The finger can detect some

differences in pulse-tension, it is true, though it is often entirely at fault, since it can only estimate total pressure, not pressure per square inch; so can the hand detect differences in temperature. But what opinion should we form of a physician who told us that he only judged of temperature by the hand and scorned the aid of the thermometer?

The best methods of estimating blood-pressure depend on the same general principle—circular compression of the upper arm by an air-pad, adjusted by an armlet not less than 12 centimetres wide, to which a manometer is attached. Air is pumped in until the pulse is obliterated at the wrist, and then cautiously allowed to escape again until the pulse just returns. Janeway regards the moment of return of the pulse-wave as the best criterion of systolic pressure; some observers take the mean between this and the point of obliteration. It is doubtful whether any apparatus accurately records diastolic pressure, but the auscultatory method will serve for clinical use. On releasing the pressure in the armlet a loud thump is heard when the stethoscope is applied below it; as the pressure is gradually lowered a point is reached where this is replaced by a muffled sound. This is taken as the diastolic pressure, which is important as being the charge which the arteries must constantly bear and from which they cannot escape. A high diastolic pressure wears an artery out more quickly than a high systolic with a low diastolic pressure.

I shall use the term 'blood-pressure' as identical with the pressure recorded by some such apparatus. Opinions differ, however, as to whether this does not represent in reality the sum of the pressure and the resistance offered by the arterial wall. Gumprecht gives physical reasons for believing that the elasticity of the tube itself does not come into the question, and Janeway concludes that, with the wide armlet, and using the first full return of the pulse as a guide, errors from thickening or calcification of the wall have little significance. This is also held by Leonard Hill, who has devised several ingenious experiments to prove the point. William Russell strongly dissents from this view. But even admitting that the record is a composite one of the resistance of the wall plus the pressure of its contents, this does not deprive it of its value, and changes of pressure as a result of treatment would still be accurately recorded.

It is impossible to discuss the whole question of blood-pressure in disease within the limits at our disposal, but we may take examples of the way in which its study has enlarged our ideas, cleared up difficulties in diagnosis, and helped in prognosis. This has naturally reacted on treatment.

It has enlarged our ideas on the subject of the 'heart failure' in acute infections. Romberg and Pässler showed that, at the height of an infection, sensory irritation and asphyxia did not produce as

large a rise of pressure as usual, while abdominal massage raised it as much as ever. It is the vessels that are involved, not the heart that is damaged. Recent work on wound shock seems to show, however, that the capillaries are the vessels chiefly concerned. And Dale and Richards have shown that capillary dilatation may occur as the result of toxic action. The term 'exæmia' has been suggested for this condition.

In the light of the knowledge we have thus obtained, it would appear that many of the stimulants employed are quite unsuitable for a condition of vasomotor paralysis. Strychnine acts on the centres, which are already exhausted or intoxicated, and therefore unresponsive. Ether has little or no effect; while brandy, which is a vaso-dilator, can hardly benefit vessels that are already relaxed. Barium salts—*e.g.*, 3 grains of the chloride—and pituitrin, which act directly on the muscle fibre, and not on nerve-endings, may sometimes help. An abdominal binder should be applied firmly to prevent accumulation of blood in the now stagnant splanchnic pool, while intravenous infusion, if carried out slowly, so as to avoid overdistending the right auricle, is often very useful.

As examples of the help which has been given in diagnosis, if we are in doubt whether a hemiplegia is due to hæmorrhage or thrombosis, we may appeal to the manometer; in the former the pressure must be high, from reasons already considered, while in the

latter it need not. Grainger Stewart has shown that the fatal issue in cerebral thrombosis is often due to a rise of pressure in the stage of reaction, or as a result of stimulant treatment, which bursts the now softened vessel. In the treatment of cerebral thrombosis, then, we must be very careful not to use any stimulant which will raise blood-pressure.

The fact that perforation in typhoid fever causes a rise of pressure, while hæmorrhage produces a fall, is one that will often be of great value in diagnosis.

In albuminuria, again, the blood-pressure will be an aid to diagnosis. In all forms of nephritis it is usually raised. Mahomed found that in acute nephritis the arterial tension rose even before albumen appeared in the urine. But in 'functional' orthostatic albuminuria, though the pressure fluctuates, it does not rise above normal. As the treatment demanded in the two conditions is quite different, it is essential to be clear which we are dealing with; and the manometer will help us. It will help us also to decide on the relative importance of albuminuria and glycosuria when they coexist.

As to prognosis, the grave import of a continued rise in pressure in cerebral hæmorrhage has already been insisted on. In pneumonia a continued but gradual fall of pressure is the rule. Gibson found that any sudden rise before the crisis implied the onset of some complication, acute delirium being often the immediate sequel, while a sudden fall was a warning of the immediate risk of cardiac (or, as I should prefer

to express it, capillary) paralysis. In Addison's disease a steady fall of pressure, despite adrenalin, has enabled me to foretell the imminence of the fatal issue. A rise of blood-pressure in pregnancy is a valuable prognostic sign of the approach of toxæmia.

It is now generally conceded that there is a stage in which the blood-pressure is raised before the structural changes of arterio-sclerosis occur, and the manometer will help us to detect it. To take an example: A busy man nearing fifty years of age, and leading the active life of his time, on walking rather smartly to catch his morning train, finds himself out of breath for some little time afterwards. On arrival at his office he has a difficulty in concentrating his mind on his work, and on rising quickly from his chair at the end of the morning he feels very giddy, and reels a little. Now, a little anxious about himself, he becomes introspective—a rare thing with him—and recalls that small worries have upset him more than they need, that responsibility has been more irksome, and that he has not felt so sure of his judgment. He tells his partner that he thinks he has been out of sorts lately, and is met with the frank reply that it is very likely, for, at any rate, his temper has been shocking. He goes to lunch, and thinks that a whisky-and-soda will put him straight. But it doesn't; it only makes him feel more uncomfortable. He lights a good cigar, and is rewarded by palpitations, instead of the blissful sensations that smoking used to evoke. He remembers now that alcohol and tobacco do not seem to have

agreed with him as they used. By the end of the day his head is aching, and he feels thoroughly worn out. He manages to eat a very good dinner as usual, however, and begins to shake off some of his fears. But his night's rest is disturbed, and next morning he feels very 'bilious,' or perhaps he has a return of the neuralgia that has been troubling him of late. It will be a good thing for him now if a violent attack of epistaxis occurs, if only to send him to his doctor. The doctor takes a heavy responsibility upon himself if he simply reassures him, tells him he is run down, prescribes some strychnine, advises a good piece of steak for lunch, and some fine old port after dinner. A more careful examination would certainly have revealed an accentuated second sound at the aortic base, and a blood-pressure of 160 to 180 millimetres; possibly also a trace of albumen, with granular casts in the urine.

The responsibility is all the greater because this man is still in the stage when treatment can be effective; and he is more likely to abide by it than the lower type of patient, 'full of coarse strength, butcher's meat, and sound sleep, who will suspect any philosophical insinuation, or any hint for the conduct of his life which reflects upon this animal existence.'

Perhaps it is even better for him if the danger-signal takes the form of an attack of hæmaturia, for he is not likely to try home remedies for this, as he may for epistaxis; nor is there much fear of the doctor treating it so lightly.

This may be simply the stage of increased blood-

pressure, without structural change, produced by toxic agents. If in this stage the patient takes less meat and no alcohol, gets more oxygen into his lungs and a better evacuation from his bowels, leads a simpler and less strenuous life, an improvement in his blood-pressure and his general condition will follow.

If this high pressure continues, a structural change will ensue. Dixon has shown that any drug which considerably raises blood-pressure will cause degeneration of the middle coat of the arteries in a healthy animal. This might happen because the same drugs which raised pressure were toxic to the arteries, or because the rise of pressure mechanically damages the wall. That the latter explanation is the correct one has been shown by Harvey, who, by merely compressing the aorta of rabbits with the fingers for two or three minutes daily, thereby raising the blood-pressure 30 to 40 millimetres, produced degeneration of the aorta above the point of compression without causing any change in the vessel below.

Tobacco is known to raise blood-pressure, and it might be thought to play a part in the much greater frequency of arterio-sclerosis in men than in women. But tolerance is easily acquired. If a man unused to tobacco smokes a cigar, his pressure first rises 10 to 25 millimetres, and then, after a quarter or half an hour, if the smoking has been continued, drops 30 to 50 millimetres, or even more. The habitual and moderate smoker under similar conditions shows no change beyond a slight rise of 4 or 5 millimetres.

According to Emerson Lee, this immunity is brought about by the production in the liver of some substance —probably a ferment—that destroys the nicotine. We therefore cannot throw much of the responsibility for arterio-sclerosis on to tobacco.

We have but a hazy notion as to the nature of the toxic substances concerned, though Barger and Dale's discovery of putrefactive bodies which raise blood-pressure has helped to clear up our ideas on the subject. The course of events may be pictured somewhat as follows: The toxin, whether formed by perverted metabolism or absorbed from the bowel, irritates the muscular coats of the smaller vessels to contraction, particularly in the splanchnic area, where it will be present in the highest degree of concentration. Finally, it is excreted by the kidney. If this condition be allowed to continue, and the irritated vessels maintain their contraction, muscular hypertrophy must occur here as elsewhere when increased work has to be done. The new muscular tissue soon undergoes degenerative changes. The increased peripheral resistance thus brought about necessitates, for similar reasons, hypertrophy of the heart. The kidney has to excrete the toxin, and suffers in the attempt, so that interstitial nephritis is apt to follow. The pressure has now to rise still more, causing more cardiac hypertrophy in order to drive enough blood through the remaining glomeruli for urinary excretion. Even so elimination becomes defective, and the toxin is therefore kept in more prolonged contact with the tissues it is damaging.

Thus, the diffuse arterial change steadily progresses. On this view the cardiac hypertrophy is purely secondary. Allbutt protests 'against the accusation of these striving hearts of complicity in the arterial disease. . . . They are stout and faithful to the end, even in defeat.'

Allbutt's convenient classification of arterio-sclerosis may be adopted. Excluding chronic Bright's disease, he holds that it is met with clinically in three forms, which, if superficially alike, are very different in nature and causation:

(*a*) *Toxic*, due to lead; to certain of the infective diseases, such as syphilis; to diabetes, and so forth.

(*b*) *Involutionary*, a senile degradation, which may appear before 'three-score years and ten.'

(*c*) *Secondary* or *hyperpietic*, the consequence of tensile stress, of excessive arterial blood-pressure persisting for some years.

The type previously described corresponds to (*c*) on this scheme. In the others there is not necessarily a rise of pressure, and we can probably refer the apparent rise, as registered by the manometer, to increased thickness of the walls. The so-called '*rise of blood-pressure in later life*,' occurring in healthy individuals, is probably due to this, and is merely an expression of that loss of elasticity which is characteristic of advancing years. The distinction between the cases in which there is a real rise of pressure and those in which there is not is a practical one. For, to quote Allbutt again, involutionary arterio-sclerosis 'results rather in the contraction of the spheres of mental and

bodily activity than, as with hyperpiesis, in the imminence of the fell sergeant Death—death by apoplexy, by cardiac defeat, or by intercurrent acute pneumonia.'

Treatment of High Blood-Pressure.

It must be borne in mind that when there are organic changes in the arteries or kidneys, the blood-pressure must be higher than normal for an adequate circulation to be maintained. In the 'pre-sclerotic' stage we should pay more attention, as Osler urges, to the peripheral field of the circulation. 'Obstruction in the fields can be overcome, to a certain point, but it is cheaper and safer to clear out the weeds. . . . We too often tinker at the pump and the mains, instead of looking at the seat of trouble in the fields.' The abiding difficulty in the treatment is that we do not know what degree of raised pressure is necessary for any degree of arterio-sclerosis, but we do know that the problem has to be met by putting the patient into the way of physiological righteousness rather than by depressor remedies.

The diet should be regulated; the bulk and number of the meals should be reduced; roasted meats, soups, and gravies should be avoided, while fruits, green vegetables, farinaceous and non-nitrogenous foods may be given freely. The salt usually added at table should be stopped, and in severe cases a salt-free diet may be advisable for a time. A pure milk diet is most useful in high-pressure cases when combined with

rest. It should be tried for a few days during periods of increments of pressure. Coffee, tea, tobacco, and alcohol should be limited, and in certain cases excluded. It is best to separate fluids from the solids, or to allow them only at the end of meals.

A warm bath taken daily on rising is a valuable adjunct to treatment. Cold bathing should be avoided. Artificial Nauheim baths, the material for which can now be readily obtained, will lower pressure, but I am not satisfied as to their advisability, as they act by vaso-dilatation. An annual course of balneological treatment is often useful. Plombières douches are recommended where there is suspicion of intestinal intoxication. These patients generally do best in a warm, equable climate for the winter.

Exercise in the open air, without strain, and not carried to the point of affecting the pulse or respiration, is followed, as a rule, by a fall in blood-pressure. A life of undue rest should be avoided, but half an hour's complete repose after the midday and evening meals should be enjoined.

These patients are apt to become unduly anxious, and their fears should be allayed as far as possible. As a rule, they should not be told the pressure reading. Particularly they should not read the index themselves, as this alone will send it up.

A free action of the bowels is, of course, imperative, since constipation increases arterial pressure both mechanically and chemically.

Potassium iodide should be given for a time, with

the view, as Leonard Williams says, 'of ferreting out such of the toxins as seem to lurk in the lymph spaces.' There is still too great a tendency to employ nitrites, which simply lower pressure by vaso-dilatation. This is, perhaps, not to be wondered at. In the early days of antipyretic drugs there was a similar tendency to indiscriminate lowering of the temperature. It is so pleasant to see some objective result from our treatment. But the rise of pressure is a symptom just as surely as a rise of temperature, and to lower either without due consideration is to side with the toxin rather than with the patient.

Sometimes hyperpiesis has to be treated, however, just as hyperpyrexia has, irrespective of the cause. Then we should select those vaso-dilators whose action is slow and prolonged. Matthew (*Quarterly Journal of Medicine*, vol. ii., p. 261) found that the fall produced by amyl nitrite was too brief to enable him to register it with the manometer. It is therefore only useful in anginal attacks. Nitro-glycerine only lowered the pressure for forty minutes. Erythrol tetranitrate, on the other hand, in ½-grain doses produced a fall lasting six hours. The great drawback to its use is, however, its liability to induce severe headache in some patients. Mannitol produces a prolonged effect also. Oliver recommends a tabloid prepared for him by Burroughs and Wellcome, having the following composition: Sodii nitrit., gr. ½; erythrol tetranitrat., gr. ¼; mannitol nitrit., gr. ¼; ammon. hippurate, gr. 1. One or two of these tabloids (designated

tabloid sodii nitrit. co.') may be taken for lengthened periods, if omitted for a few days or a week in each month. In one case the pressure fell in seven days from 210 to 160, and was still found to be 160 after twelve months' treatment. I have found benefit from ammonium hippurate in larger doses—3 to 7 grains three times a day. From the early appearance of atheroma in myxœdema thyroid extract is often prescribed in cases of arterio-sclerosis with high pressure, and I have come to rely upon it considerably in doses of ½ to 1 grain three times a day. Indeed, according to some authorities iodide merely acts in arterio-sclerosis by stimulating the secretion of the thyroid gland.

There is a great difference in the response to treatment. In some cases the results are remarkably good, and patients have been restored to years of useful and active life.

CHAPTER XIV

ON CYANOSIS AND DYSPNŒA

The essential cause of cyanosis is an abnormally large amount of reduced hæmoglobin in the capillary blood, while the essential cause of dyspnœa is excess of carbon dioxide or some abnormal acid in the respiratory centre. It will follow that, although these two conditions are often associated, this is not necessarily the case. Thus in uræmia we may see dyspnœa without cyanosis, whereas in congenital heart disease cyanosis occurs without dyspnœa. As Lewis points out, if a patient is urgently breathless and an equivalent cyanosis is not found, the dyspnœa is not wholly due to deficient aeration of the blood. Non-cyanotic dyspnœa is produced by the presence of abnormal acids in the blood, such as diacetic acid in diabetic coma, acid sodium phosphate in uræmia, and lactic acid in various conditions.

Mere diminution in the amount of oxyhæmoglobin is not sufficient to cause cyanosis. Thus in coal-gas poisoning the corpuscle contains less oxygen, and yet there is no cyanosis, for the new compound, carboxyhæmoglobin, is a bright cherry-red.

But if enough of the hæmoglobin is reduced or is in

the form of methæmoglobin or sulphæmoglobin, there is cyanosis. In the chapter on Intestinal Intoxications, it was shown that nitrite-producing microbes in the intestine may cause methæmoglobinæmia or sulphæmoglobinæmia, which may lead to a striking degree of cyanosis. Certain coal-tar drugs may also be responsible for the former condition. Either can readily be detected by the spectroscope. It is needless to repeat what has already been said, beyond urging the necessity of diagnosing these toxic conditions from ordinary cyanosis.

Ordinary cyanosis becomes perceptible as soon as there is about 5 grammes of reduced hæmoglobin per 100 c.c. of blood. It depends on the absolute concentration of reduced hæmoglobin rather than on its ratio to oxyhæmoglobin. Thus anæmic individuals with less than 5 grammes of hæmoglobin per cent. cannot become cyanotic. Cyanosis is also influenced by the thickness of the epidermis and the amount of pigmentation, but still more by variations in the number, width, and length of blood-filled capillaries per unit of surface; thus it is increased by stasis.

Lundsgaard and Van Slyke classify the causes of true cyanosis somewhat as follows:

1. Although all the air traverses lung tissue which is anatomically accessible to inspired air, diffusion of oxygen is hindered by—(1) low oxygen tension in the alveoli occurring at high altitudes or resulting from shallow breathing, as in pneumonia; (2) decreased permeability of the alveoli due to physical conditions such as the exudation of fluid into them.

2. Part of the blood passing from the right heart to the arteries traverses a path to which access of air is anatomically impossible; as, for instance, when there is a patent foramen ovale in the heart.

About one-third of the total blood may be shunted through an unaerated path before sufficient unsaturation results to cause cyanosis. Presumably the reason for the absence of cyanosis when even one entire lung is collapsed by pneumothorax or pleural effusion is that less than half of the blood then flows through the unaerated lung. When the pressure in the pleural sac rises sufficiently to obstruct the circulation through the pulmonary artery on this side, more blood passes through the sound side, which may become overventilated. The blood may, therefore, still be 96 per cent. saturated with oxygen.

3. There may be increased reduction of the oxygen in the blood, either from decreased rate of flow or from increased rate of oxygen consumption by the tissues.

The principal causes of cyanosis, therefore, appear to be interference with diffusion in the lungs, shunting of unaerated blood into the arteries without passing through normal lung, and slowing of the capillary flow

Nature's method of compensating for defective oxygenation of existing corpuscles is by adding to their number. Thus prolonged residence at high altitudes, such as Quito in Ecuador, results in polycythæmia. The diminished oxygen tension at that height necessitates an increase in the number of oxygen-carriers, so that, though each is capable of carrying

less, the total amount of oxygen carried to the tissues remains the same. Applying this to diseases associated with chronic cyanosis, we should expect to find polycythæmia also. Conversely, polycythæmia in itself tends to produce cyanosis, for, as we shall see, by slowing the capillary circulation, it increases the reduction of hæmoglobin. And when there is excess of hæmoglobin the limit of 5 grammes in the reduced state will be reached more easily.

Erythræmia (Splenomegalic Polycythæmia).—The most striking example of increase in the red corpuscles occurs in the condition first described by Vaquez in 1892. Our knowledge of this disease has been added to by the observations of Osler, Saundby and Russell, and Parkes Weber. The patient is usually in the middle period of life. He is generally, though not invariably, cyanosed, but there is no respiratory distress. The eyes may be prominent and the conjunctivæ suffused. Examination of the blood shows that the red corpuscles are increased from the normal 5,000,000 to a figure varying between 8,500,000 and 12,000,000 per cubic millimetre, while the hæmoglobin is raised to 120 or 150 per cent. The white corpuscles are usually increased from the normal 8,000 to 20,000 per cubic millimetre, but in some cases are actually diminished. The viscosity of the blood is naturally considerably increased. The spleen is usually enlarged; sometimes it is greatly enlarged, but then infarcts or tubercles have usually been found. The urine frequently contains a trace of albumen.

Pigmentation of the skin has been noted. The most prominent symptoms are torpor, both mental and physical; a sensation of fulness in the head, with headache and vertigo, and in some cases nausea and vomiting. As Osler has pointed out, these symptoms remind us of those to which mountain-climbers and aeronauts are liable. There are also certain vaso-motor symptoms. If any part be rubbed it goes red, and if the patient gets hot the general cyanosis is apt to be replaced by a general flushing. A dependent part becomes blue, but if it be held up it may become pale. The vessels must be very full, for the volume of the blood is increased. Now the capacity of the vessels may be increased by relaxation of the vasomotor tone, and this loss of tone causes the effect of gravity on the circulation to become more pronounced. By the relaxed state of the vessels we can also explain the fact that the blood-pressure is not necessarily raised, although the vessels are so turgid.

The increased viscosity of the blood is a necessary result of its concentration by excess of red corpuscles. Gustav Mann has calculated that the maximum number of corpuscles which the blood is capable of holding in each cubic millimetre is 18·9 millions. A blood-count of 12,000,000 implies, then, a very great increase in the viscosity of the blood, and therefore a considerable delay in the circulation time through the capillaries. This has been experimentally demonstrated. Anything which increases the stay of the blood in the capillaries allows of the abstraction of more

oxygen from it. We should therefore expect that this cause of cyanosis would be diminished in part by stimulating the rate of the circulation by warmth and friction, as is actually the case.

The polycythæmia remains to be explained. There is certainly an increase in the erythroblastic tissues in the red marrow. This could arise in two ways. Either it is compensatory or it may be of the same nature as a new growth. This latter view has been put forward by Parkes Weber (*Quarterly Journal of Medicine*, vol. ii., p. 85). He gives good grounds for thinking that the change in the red bone-marrow is primary; that there is an over-production of red cells, just as in myelogenic leukæmia there is an over-production of white cells.

There is no evidence that this change is compensatory. The cyanosis is not due to an abnormal reducing agent in the blood, as was shown by Boycott, nor is there any reason to suppose that it is other than the result of slowing of the circulation by increased viscosity of the blood.

Treatment.—There is at present no effective treatment for this disease. That oxygen inhalations are no good is only to be expected, as there is no deficiency of oxygen in the blood. Temporary benefit may be derived from bleeding. X rays have been applied to the long bones with benefit in some cases. As benzol is believed to destroy blood-corpuscles, I have given 5 to 10 minims in a capsule twice or thrice a day with apparent benefit.

Cyanosis in Congenital Heart Disease.—During fœtal life the circulation is so arranged that the purest blood

from the placenta is sent as quickly as possible to the head. To achieve this the liver is short-circuited by the ductus venosus, and the blood entering the right auricle is directed by the Eustachian valve through the foramen ovale into the left auricle. In this process the limbic bands of the auricle assist by drawing the inferior vena cava towards the foramen. From this point the adult course of the circulation is followed to the head. The returning stream enters the heart by the superior vena cava, and passes down into the right ventricle, being largely shut off from the other stream in the right auricle by the Eustachian valve and the limbic bands. It leaves the right auricle by the pulmonary artery, but as it is unnecessary for all this volume of blood to go to the lungs, it is diverted by the ductus arteriosus into the aorta beyond the origin of the carotids.

It is not correct to attribute the child's first breath to the stimulating effect of exposure to the lower temperature of the outside world, for interference with the placental circulation while the child is still *in utero* will cause it to breathe; and if the child be received into a bath at body temperature, respiratory movements will occur as usual. When oxygenation in the placental circulation is interfered with, carbon dioxide accumulates in the respiratory centre, and produces its usual effect—a stimulus to respiratory movements.

These movements aspirate a large volume of blood into the lungs, which returns by the pulmonary veins

to the left auricle. A fall of pressure, therefore, occurs in the right auricle, and a rise of pressure in the left, which helps to close the oblique opening in the foramen ovale. The downward movement of the diaphragm alters the plane in which the limbic bands act, so that they no longer draw the inferior vena cava towards the foramen ovale.

The alterations in pressure also help to close the ductus arteriosus, as the distended aorta now projects within its lumen, and stops the flow through it.

In this way the ordinary post-natal condition is arrived at. But if there be stenosis at or below the pulmonary valves, the mechanism of this change is fundamentally disturbed, though the fœtal circulation will not have been embarrassed in any way. The pressure on the right side of the heart will be too great to allow of closure of the septum between the two sides, so that it remains patent either in its auricular or its ventricular portions. In the latter case there is probably a true congenital defect, a reversion to the type of reptilian heart; while the former is commonly the necessary result of a fœtal endocarditis.

The deficiency in the exit of blood from the right ventricle will be made good to some extent by the ductus arteriosus remaining open. I have seen complete atresia of the pulmonary valves, in which the whole of the blood to the lungs reached them by this route.

The only way in which the body can compensate for this obstruction of the pulmonary artery is by

charging the blood more highly with corpuscles, so that the oxygen capacity of that portion which does reach the lungs will be increased. Polycythæmia is therefore always met with in such cases, and may amount to 8,000,000 or 9,000,000 per cubic millimetre. This, by slowing capillary circulation, adds to the cyanosis.

It has been contended that the polycythæmia and cyanosis are alike due to general congestion of the venous system from obstruction; but it has probably been the lot of everyone, as it certainly has been mine, to see cases of congenital heart disease with marked cyanosis and a high degree of polycythæmia, in which signs of back-pressure were entirely lacking.

Other causes of chronic cyanosis call for only brief consideration. The other cardiac lesions typically associated with cyanosis are diseases of the tricuspid valve and adherent pericardium. Here the distribution to the lungs is at fault, so that oxygenation is imperfect; at the same time venous congestion causes a certain degree of stasis in the capillaries, so that the blood there is richer in corpuscles than normal. If œdema be present also, this will increase the concentration of the blood. In this way a moderate degree of polycythæmia is found in the blood obtained from the peripheral circulation. This is spoken of as a relative polycythæmia, since there is not an absolute increase in the number of corpuscles, but only an alteration in their distribution with respect to the fluid constituents.

Mediastinal inflammation and growths act in very much the same way, by interfering with the diastolic filling of the heart.

Of all pulmonary conditions, emphysema causes the highest degree of chronic cyanosis. According to Osler, cyanosis of an extreme grade is more common here than in any other affection, except congenital heart disease. 'So far as I know,' he said, 'it is the only disease in which a patient may be able to go about, and even to walk into the hospital or consulting-room, with a lividity of startling intensity. The contrast between the extreme cyanosis and the comparative comfort of the patient is very striking. In other affections of the heart and lungs, associated with a similar degree of cyanosis, the patient is invariably in bed, and usually in a state of orthopnœa.' He made another exception in favour of toxic cyanosis.

In emphysema there is such a gradual diminution of the oxygenating surface of the lung that the discomfort to the patient is reduced to a minimum. There is only a moderate polycythæmia, however. After emphysema, fibroid change in the lung is, perhaps, the most important cause of marked chronic cyanosis. Here again the diminished surface available for respiratory interchange is responsible.

When, in these conditions, the right heart begins to fail, cardiac causes for cyanosis are superadded, and the dyspnœa becomes marked. Until then the right heart has an extraordinary power of compensating for increased resistance in the pulmonary circulation.

In pneumonia, cyanosis was generally attributed to failure of the right heart rather than to the consolidation of the lung with consequent insufficient oxygenation. But the 1918 epidemic of influenza showed many striking examples of cyanosis before heart failure occurred, which led to reconsideration of the problem. It was noted that in such cases very little air extends the affected lung. Keene and Winternitz showed by injecting the lung through the pulmonary artery that only a very scanty colour was produced in the consolidated portion, whereas the normal parts were deeply stained. By means of X-ray examinations of human lungs injected with barium emulsion, Gross found that the vessels in the region of grey hepatization were almost impassible. An important factor in pneumonia cyanosis would, therefore, appear to be deficient oxygenation.

Oxygen can produce a striking alleviation of cyanosis in emphysema with failing heart. This contrasts with its failure in congenital heart disease, and provides a further argument against explaining the cyanosis in that condition as due to venous congestion.

Local cyanosis, such as occurs in Raynaud's disease and other vasomotor diseases, appears to be due partly to increased capillary distension and partly to stasis, allowing of increased absorption of oxygen by the tissues. Traumatic cyanosis, which is seen in the rare condition of pressure stasis following severe crushes of the chest, has been shown by Beach to be due to mechanical over-distension of the veins and capillaries.

True extravasations of blood may occur as well, however, especially in the lax tissues around the eye, where the ordinary changes of colour in bruises will follow.

Conclusions.—Toxic cyanosis is due to a chemical change in the hæmoglobin molecule, produced by drugs or intestinal intoxication, and leading to the formation of methæmoglobin or sulphæmoglobin. It is not associated with polycythæmia, and there may be marked oligocythæmia.

True cyanosis from increased reduction of hæmoglobin in the red corpuscle is typically associated with polycythæmia, which may be—

1. *Absolute* where there is simple defect of oxygenation, either—

(*a*) In the lungs, because some of the blood does not get there, as in congenital heart disease, or because there is reduction in the oxygenating area of the lungs, as in emphysema; or,

(*b*) In the periphery, because slowing of the circulation allows more reduction of oxyhæmoglobin to occur in the capillaries, as in erythræmia; or,

2. *Relative*, from anasarca, which causes concentration of the blood, as in failing heart, or in a heart embarrassed by pericardial adhesions, which interfere with its filling.

I would emphasize, in conclusion, the assistance that the blood-count and the spectroscope will give in making the diagnosis on which alone correct treatment can be based.

Dyspnœa.—A healthy man may become short of breath from two different causes—by taking strenuous exertion, or by going to a high altitude. Now these two ways illustrate the two main types of dyspnœa in disease. We may say that an athlete who is 'breathless' has incurred an oxygen debt. Muscular contraction can take place in the entire absence of oxygen, for this is only needed for the recovery process. Glycogen supplies the requisite energy for contraction by breaking down into lactic acid, hexose diphosphate being the intermediate stage. But oxygen is immediately needed to rebuild the lactic acid into glycogen, oxidizing one quarter of it in the process. When exertion does not produce dyspnœa, it means that the intake of oxygen balances the production of acid; but if muscle were unable to run into debt for oxygen, our capacity for exertion would be limited indeed. As long as this debt is unpaid, lactic acid is present in the blood stream, increasing its hydrogen-ion concentration; in other words, there is acidæmia which stimulates the respiratory centre to renewed effort. If the debt piles up enough there is fatigue sufficient to stop the exertion, which is protective in that it allows of recovery taking place without incurring fresh expenditure. Rigor mortis is oxygen bankruptcy. The continuance of dyspnœa after exercise indicates that the oxygen debt is not yet paid off (A. V. Hill, Meyerhof). In the corresponding type of breathlessness in disease, there is increased hydrogen-ion concentration in the blood, due to lactic acid or some

other substance. Thus we have seen that in uræmic dyspnœa it is probably due to acid sodium phosphate. Even when in the ketosis of diabetes there is no acidæmia, a chemical substance is present which similarly stimulates the respiratory centre. There will be no cyanosis until the heart begins to fail.

On the other hand, at high altitudes the mere lack of oxygen due to its low tension in the atmosphere directly stimulates the respiratory centre, nervous tissues being more sensitive to this lack than any other tissues. The resulting hyperpnœa washes out CO_2 from the lungs, so that the blood tends to be more alkaline, a condition which the kidney tries to rectify by excreting more alkali. The dyspnœa of heart disease is due to oxygen lack, largely the result of capillary stasis which allows of more complete reduction of hæmoglobin. It is therefore usually associated with cyanosis; but there need be no increased production of acid. Indeed, the increased pulmonary ventilation may actually produce alkalæmia.

'This broad distinction between cause and effect may be recognized—when acidæmia is associated with breathlessness, the acidæmia is the cause of the breathlessness; when alkalæmia is associated with breathlessness, the breathlessness is the cause of the alkalæmia . . . Just as the dyspnœa of exercise is the type to which acidæmic forms of dyspnœa may be referred, so the dyspnœa of high altitudes is the prototype shown in normal individuals of the alkalæmic forms.'

Treatment.—It follows that if dyspnœa is associated with acidæmia, administration of alkali to increase the alkaline reserve of the blood may be helpful. Its limitation in the case of diabetic ketosis have already been considered. But when dyspnœa is associated with alkalæmia, as it usually is in simple cardiac cases, it is clearly futile to give alkalis. If digitalis is not contra-indicated on other grounds, it should be tried in such cases because a cardiac tonic will help to relieve capillary stasis and the consequent anoxæmia.

Naturally both in cyanosis and dyspnœa treatment by oxygen seems the rational procedure. But as already pointed out, when the cyanosis is due to the shunting of unaerated blood from the right to the left side of the heart, as in congenital heart disease, oxygen will be of no avail. In failing heart, it will not be so effective as digitalis when capillary stasis is responsible for the oxygen lack, but when pulmonary complications, such as congestion and œdema, are present it will be very helpful. In pneumonia it is particularly indicated. The failure of oxygen inhalations is often due to the method of administration. As formerly given, they had no effect in increasing the inadequate oxygen content of the blood. Dr. Hilton informs me that his observations show that when the funnel of an oxygen cylinder is 10 centimetres distant from the mouth, oxygen has no advantage over ordinary air. But when the funnel is placed right over the mouth and nose the effect on the alveolar oxygen is almost identical with that obtained by the nasal catheter, and is more

comfortable. By this latter method a rubber catheter is introduced through the nose into the naso-pharynx. The catheter is attached to a Wolff bottle containing warm water through which oxygen is bubbled. According to Meakins, in order that sufficient oxygen shall be administered, it must enter the bottle through a tube of at least 1 centimetre bore, and the bubbles must be so rapid as not to be countable. The Haldane mask and oxygen bag is far more efficient, but some patients cannot tolerate it.

That oxygen given in this way can definitely benefit the oxygen desaturation of the blood has now been proved by arterial puncture. This allows of direct measurement of the percentage of oxygen in the blood before and after treatment.

CHAPTER XV

THE PROBLEMS OF ASTHMA

The problems of asthma were for years most baffling, but recent work has cleared the ground and defined the issues. These problems have now revealed themselves as involving subjects of most topical interest —psychotherapy, sensitiveness to foreign proteins, vagotonia and endocrine balance. The treatment of asthma summarizes in itself, as it were, the chief trends of modern therapy. But there has been a tendency on the part of enthusiastic workers in some one of these fields to neglect due consideration of the other aspects. Successful treatment involves them all.

It is always a dangerous thing to try to express a disease in a formula. Nevertheless, I attempted to do so for asthma not long ago. Hurst has recently improved upon that formula, and I accept his emendation gladly. He has defined asthma as due to an unstable or irritable condition of the bronchomotor portion of the vagus nucleus, which causes it to react unduly to psychical or peripheral stimuli, or to foreign proteins in the circulating blood. I think this could still be modified with advantage by including the obvious vasomotor turgescence which accompanies the

bronchomotor spasm, as this is always present, and is sometimes the most striking feature of an attack, just as it is in the closely allied condition of hay fever. Moreover, it is carried out by the same vagal mechanism. Thus modified the formula can be expressed diagrammatically as follows:

$$
\begin{tikzcd}
 & \text{Psychical stimuli} \arrow[d] & \\
\text{Peripheral stimuli} \arrow[r] & \text{Vagus nucleus} \arrow[d, dash] & \text{Foreign proteins} \arrow[l] \\
\text{Bronchomotor spasm} & {} \arrow[l] \arrow[r] & \text{Vasomotor turgescence}
\end{tikzcd}
$$

I will first consider the stimuli acting on the centre, and then some features of its response.

(1) **Psychical Stimuli.**—That asthma often occurs in neuropathic families, and that asthmatics are unduly suggestible, are well-known facts. The paroxysm excited by an artificial flower figures in every text-book. But it is extraordinary to witness the almost instantaneous relief that may follow a hypodermic injection of distilled water into a patient who is anticipating one of adrenalin, when this is known to be efficacious. It makes me wonder how much of the success of single minim doses of adrenalin are due to suggestion and how much to the drug. At any rate, it explains why the asthma curer who has profound belief in the efficacy of his treatment finds increasing justification for that belief. For his confidence arouses responsive confidence in his patient. But what is not so clearly

recognized is that the effective stimulus often arises from a psychic conflict. Such a conflict may express itself at the psychic level of the nervous system as an obsession or a phobia, and at the sensori-motor level as a paralysis, a tic, a contracture or an anæsthesia; while if it sinks deeper to the visceral level it may express itself as glycosuria, exophthalmic goitre or asthma. Naturally other influences will help to decide in which of these ways the psychic trauma reveals itself. Thus, one sufferer from a psychic conflict who has to face a hostile environment may escape through an hysterical paralysis, but another who has to face the internal disorder produced by sensitiveness to foreign proteins is more likely to develop asthma.

(2) **Peripheral Stimuli.**—I have little to add to the common stock of knowledge of this subject. The influence of eyestrain, hay fever and other nasal troubles, sinus infection, gastric and intestinal disturbances, and of uterine disorders is well recognized. But I should like to call special attention to enlarged bronchial glands, especially in children, and to suggest that this may explain the liability of healed tuberculosis to excite asthma in susceptible subjects. Interesting observations by Baccarini show that peripheral irritation of the pleura, such as paracentesis, may excite an attack of asthma. In the epileptic a fit can be similarly produced, which leads him to compare bronchial spasm to a localized epilepsy. Other points of resemblance between epilepsy and asthma will readily occur to the reader.

(8) **Foreign Proteins.**—Of recent years great attention has been paid to this factor. Morley Roberts has made the profound remark that 'immunity is assimilation.' There is one flesh of birds and another of beasts. From the welter of amino-acids which result from the disintegration of food proteins each animal has to build up its own characteristic and specific tissues. Specificity is chemical as well as morphological. To some foreign proteins we are naturally immune—*i.e.*, we can assimilate them automatically; to others we acquire immunity—*i.e.*, we learn to assimilate them. But to some foreign proteins immunity is neither congenital nor acquired. The tissues continue to resent the intrusion of such. They will not assimilate them. Such proteins excite anaphylaxis in varying degrees. Richet has defined anaphylaxis as the last stand of the race against adulteration of its protoplasm. In extreme degrees anaphylactic shock is fatal because assimilation would mean too profound an alteration of bodily structure. In less degrees anaphylaxis declares itself in violent attempts to get rid of the foreign invader. As Drury has expressed it, the toxic idiopathies are conservative, self-repairing mechanisms under parasympathetic control.

The Influence of the Parasympathetic.—The great function of the parasympathetic may be defined as promoting the assimilation of suitable and the rejection of unsuitable material. Thus it starts the secretory and muscular processes of digestion, while it empties the rectum and bladder, and can reject food by vomit-

ing. The excitation of bronchial catarrh and cough is similarly a method of ridding the body of unsuitable material, and it is interesting to recall in this connection that drugs which are expectorant in small doses are emetic in larger ones. The similarity of the parasympathetic action on the alimentary and respiratory tracts is not surprising when we remember that the latter tract develops as an outgrowth from the former. The vagal factor in normal respiration may indeed be defined as a mechanism for insuring the alternate taking in of assimilable oxygen and the rejection of unnecessary CO_2. Confronted with an irrespirable gas the vagus checks its entrance to the lungs by larnygeal spasm. But I do not think we can in this way explain bronchomotor spasm, which, while tending to interfere with elimination, does not prevent the entrance of unsuitable material. This, I think, is an example of that exaggerated response which is so typical of pathological states. The undue irritability of the vagus centre sets up such a strong efferent impulse that it is not confined to the vasomotor channels, but overflows along the bronchomotor fibres.

Without accepting the whole of Eppinger's and Hess's theories we may agree that the asthmatic is a vagotonic, and is liable to other manifestations of vagotonia. I recently had a curious instance of this in a man who suffered from both asthma and gastric ulcer, and who had found out for himself that he could relieve the pain of his ulcer by smoking a stramonium cigarette. And I should agree with the description

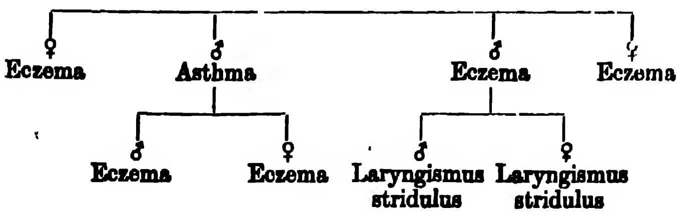
which has been given of a form of mucous colitis as 'asthma of the colon.'

The Sympathetic and Endocrine Balance.—But vagotonia may be relative as well as absolute. In other words, it may well be that an overacting vagus is due to diminished action of the antagonizing sympathetic. One of the greatest gaps in our knowledge at the present time is our almost total ignorance of the part played by the endocrine glands in immunity. Yet I feel that further research will show that just as anaphylaxis is associated with vagotonia, the opposite condition of sympathicotonia is related to immunity through the endocrine system. Not infrequently hypo-adrenalinism follows or accompanies anaphylaxis, and certainly adrenalin has a valuable action in anaphylactic shock. It has a similar effect in some cases of urticaria. Hurst considers that the toxic idiopathies, including asthma, produce their effect, at any rate in part, by depressing adrenal activity. He believes that the influence of fatigue in inducing the asthmatic paroxysm is capable of a similar explanation. Morley Roberts suggests that so might be the apprehensiveness so common in asthmatics. As explained in Chapter I., the over-activity of the broncho-constrictor fibres of the vagus is kept in check by the broncho-dilator action of the sympathetic, which the secretion of adrenalin would stimulate. Hence the effect of an injection of adrenalin, or of sudden fright in checking an attack of asthma. Asphyxia has a similar action and produces the same

effect; no doubt it is thus a factor in bringing the attack to an end without a fatal issue. I am aware that Stewart and Rogoff deny this emergency action of adrenalin, but Cannon's recent experiments (*Journal of Mental Nervous Diseases,* 1921, liv., p. 421) have disposed of much of their purely destructive criticism. The liability of asthma to come on during sleep, when the parasympathetic gains the upper hand, further points to the influence of disturbed balance between the two great branches of the visceral nervous system. The reinforcement of the adrenalin effect by pituitrin may be held to point in the same direction. The glands which co-operate with the sympathetic appear generally to help in checking the asthmatic paroxysm. The stimulating effect of the gonads in the sympathetic endocrine group may account for the influence of uterine disease in exciting asthma. It must be admitted, however, that it is difficult on this hypothesis to explain why asthma is liable to appear at puberty and to be aggravated by pregnancy, when the thyroid and pituitary are stimulated, unless it is that some asthmatics have a gonadal deficiency which declares itself in this way. Certainly gonadal deficiency may be associated with thymic asthma, which is comprehensible since the thymus is an infantile organ, apparently antagonistic to the gonads. Recently I saw a case of what appeared to be thymic asthma in a stout girl aged seventeen, with amenorrhœa. Treatment with an ovarian extract was sufficient to stop the attacks. No element of suggestion came in here, for she did

not know what she was taking. In general terms, it would appear that when the endocrine balance sways in the direction of the vagus, asthma is likely to occur in susceptible subjects; when the balance is redressed in favour of the sympathetic, attacks may be cut short or prevented.

Asthma, Anaphylaxis and the Skin.—The skin undoubtedly has excretory functions. Uræmia may manifest itself by a marked toxic erythema. The rashes of the exanthemata have often been compared with that produced by serum in anaphylactic subjects. This conception of an excretory mechanism is expressed in the popular idea of the benefit derived by 'getting the rash out.' The toxin which cannot be assimilated —*i.e.*, to which the body is not immune—must be got rid of somehow, and at any rate from the vital structures. In this connection it is interesting to note the occasional alternation of attacks of eczema and asthma. The following family tree which came under my notice is a striking example of this alternation in different members of the family:



The condition of laryngismus stridulus is recognized as the infantile equivalent of asthma. It is further

of interest to recall that both in skin diseases and in asthma eosinophilia is a usual feature of the blood picture. As an attack of asthma goes on and expectoration becomes more abundant, the eosinophils pass into the sputa. I should regard the skin reaction of an asthmatic to foreign proteins as an attempt to wash out the offending non-assimilable material from the skin. I was proceeding to look for the occurrence of eosinophilia in the urticarial wheals produced by this test, when Dr. Mackenzie Wallis informed me he had already observed it. I think this all accords with the observations of Kanthack and Hardy, thirty years ago, on the rôle of eosinophilia in bacterial infections and intestinal digestion, which have passed into undeserved oblivion.

Treatment.—These considerations help to provide a rational explanation for some methods of treatment which have been empirically used in the past. I hope also that they may help to co-ordinate the views of those working at different aspects of the problem, and to emphasize the necessity for all-round assault on every case of asthma from these various aspects. For some, asthma is merely a psychological problem; but that is to close one's eyes to the toxic factor. For others the toxic element is the primary thing, the nervous factor being merely the failure of the nervous system to co-operate successfully in getting rid of the toxin. This view has been well expressed by Morley Roberts thus: 'Why is there a spasm? What *is* the spasm but violent overacting surface tension pulling every cell in the small bronchi and alveolar spaces into its least form,

as it tries to squeeze out irritants, tries to defæcate, so to speak. The sympathetic and parasympathetic rush in to aid. There is a tendency to overrate nervous action. Cells live their lives, have their disasters, even without nervous interference except in stress, as they did in the beginning.' But this view is not capable of explaining the influence of suggestion in actually producing a paroxysm in the absence of the exciting toxin. The suggestibility of the patient should be utilized to help him confidently to expect a cure. The effect of climate may often be due to suggestion. An asthmatic goes to a place and has an attack; therefore, each time he goes there he expects to have one, and has it. The converse is also true. To point this out in the former instance may help him to avoid repetition. But search must also be made for deeper seated psychological troubles. Naturally sources of peripheral irritation must be eliminated; this includes avoidance of late suppers and cold bedrooms. The skin reactions are in my experience very helpful in determining the foreign proteins to which the patient is sensitive. Not only in asthma should this be tried; it is worth trying in any vagotonic with toxæmic symptoms. I recently had a striking example of this in a patient who was emaciated and profoundly depressed, but whose chief objective trouble was a painful swelling of the tongue and lips. Dr. Mackenzie Wallis kindly tested his skin reactions and found he was highly sensitive to cereals. In addition to other simple measures, cereals were removed from his diet, and he

was allowed many things which had formerly been prohibited in the belief that he had gout. The effect was dramatic; in one month he put on 16 pounds in weight. His medical man wrote as follows: 'I think his almost daily progress has been one of the most marked and interesting cases I have had under my observation for a long time. Socially he is entirely altered . . . bright and entertaining, and his old-fashioned courtesy has returned. In fact, he is so far a complete revolution and revelation.' An experience like that gives one cause to think of the toxic factors we must often overlook in cases diagnosed as neurasthenia, or 'functional.' Where the offending protein cannot thus be eliminated, we should consider what methods of desensitization are feasible. I should like to add that in my experience it is most important to exclude the syphilitic toxin as the offending protein. I saw a case in a woman, aged forty, who had asthma during her last pregnancy; she was delivered of a macerated fœtus and her Wassermann reaction was strongly positive.

The universal belief in the efficacy of the belladonna group in asthma finds its justification in the paralyzing action of such drugs on the parasympathetic endings, just as the fillip given to the sympathetic by adrenalin or cocaine helps to redress the balance in another way. According to some, the influence of iodide is mainly to activate the thyroid; if this is so the benefit of this drug in asthma is comprehensible, since the thyroid secretion lowers the threshold to sympathetic stimulation. But so far we have no explanation of the way in which arsenic

acts in this disease, though certainly it often seems to help. The importance of doing everything we can to restore an impaired endocrine balance is, I think, undoubted. In young subjects breathing exercises to develop the chest are also valuable.

This all-round attack on the problems of asthma seems to me to afford the best chance of relief, especially if carried out before structural changes such as emphysema have occurred. After that a vicious circle is set up which is hard to break.

CHAPTER XVI

VITAMINS AND CALCIUM METABOLISM

At the end of the nineteenth century it was held that the calorie value of the food consumed was the all-important factor in nutrition. Then Hopkins showed that a dietary of pure protein, fat and carbohydrate, with the addition of appropriate mineral salts, could be well digested, normally absorbed and duly oxidized in the body of an animal, and yet wholly fail to support it in the absence of certain organic substances present in minute quantities, and easily overlooked. Funk believed that he had isolated some of these as basic crystalline bodies and therefore called them *vitamines*. It is now agreed that they have not yet been prepared in a pure form, and as there is therefore no satisfactory evidence of their amine constitution, the non-committal term of *vitamin* has been substituted. They are as characteristic of vegetable activity as hormones are of animal life, and, like hormones, they are intensely active in minute quantities. As they are introduced into the body with the food they have been appropriately called exogenous hormones. Their influence on the endogenous hormones has been insisted on by McCarrison.

It is usual to follow McCollum in classifying them as

(1) Vitamin A, the fat-soluble vitamin concerned with growth and containing the anti-rachitic factor, (2) vitamin B, the anti-neuritic substance, and (3) vitamin C, the anti-scorbutic factor. The minimal amount of a particular vitamin which is require to prevent or remove such symptoms in an animal has been determined (Osborn and Mendel, Drummond and Zilva, Mottram). Although more abundant in fresh, uncooked food, they are not destroyed by heating to boiling if access of oxygen be avoided, and are therefore more stable than enzymes. There does not seem to be any special advantage in increasing the intake of them above the normal. Above the minimal amount their action appears to be qualitative rather than quantitative.

Vitamin A.—The absence of the fat-soluble vitamin from vegetable fats is due to its being left behind in the vegetable structures from which such fat is derived. Thus if margarine is made wholly from vegetable fats it lacks this vitamin. It is abundant in butter, and is present in most animal fats, with the exception, strange to say, of lard. Mellanby, who was the pioneer in the modern work on rickets, tested the influence of different fats in remedying this condition when experimentally produced in puppies. He found that the effect varied with the amount of vitamin A contained in the fat. Cod-liver oil is particularly rich in it, which is interesting in view of its time-honoured empiric use in the treatment of rickets.

Now rickets is a disease of growth, and if the animal does not grow the typical bony changes do not occur.

Since vitamin A is necessary for growth, its complete absence is not accompanied by rickets simply because growth is checked. But if cod-liver oil is oxidized by a current of air, it fails to support growth while still potent as a prophylactic against rickets. Evidently there is more than one active ingredient in the oil. Further, rickets is a disease of winter, and it has been found that sunlight or the ultra-violet rays from the mercury vapour quartz lamp provide the requisite actinic rays to mobilize the residual stores of the vitamin already in the tissues. Even the air which has been previously irradiated may have a similar effect (Margaret Hume), which may explain the importance previously attached to fresh air in this connection. There is a sort of inverse relationship between the amounts of vitamin A and light that are necessary to regulate the mineral metabolism of the body. Thirdly, there must be in the diet an adequate amount and correct balance of calcium and phosphates. An actual deficiency in this respect is not likely to occur, however, on any ordinary diet, and within limits a sufficiency of the vitamin is able to correct for this. Deficiency of this vitamin or of calcium in the mother's diet during pregnancy and lactation may also predispose the offspring to rickets. The whole question of these interesting interactions is full of promise for the solution of other metabolic problems, and may be studied in the reports of the Medical Research Council, where the valuable observations of Miss Chick and her fellow-workers in Vienna are fully recorded.

Another curious result of deprivation of vitamin A is

xerosis of the eyeball and conjunctiva, due to damage of its entire secretory apparatus.

Vitamin B.—This water-soluble vitamin is the substance which is necessary for the prevention of beri-beri, and which rice loses when it is polished.

In the 'refining' of the wheat grain before it forms white flour the water-soluble vitamin is entirely removed. If in this country pure white wheaten flour were to form so large a proportion of the whole diet as rice does in the East, beri-beri would with certainty appear among us. Brown bread and butter is, from the standard of vitamin supply, an excellent combination, while white bread and margarine may be a very bad one.

Vitamin C.—The experience of the war has quite deprived lime-juice of its reputation as an anti-scorbutic. This reputation dates from less scientific times when all fruits of this kind were known as 'limes.' The 'lime-juice' of the Navy was obtained first from the Mediterranean area, where the true limes do not grow. During the Napoleonic wars it was difficult to get fruit from the Mediterranean, and just then we wished to develop the newly acquired West Indian Islands, where limes grow but not lemons. Quicker voyages, cold storage, and other improvements prevented serious outbreaks of scurvy until the siege of Kut. The Hindoo troops would eat dried grain but no meat, and in spite of lime-juice the death-rate from scurvy was so high as to be an important factor in the fall of Kut. The British troops ate horse-flesh and survived.

Fresh milk contains both an antiscorbutic and an anti-neuritic principle. Sterilization of milk destroys the former, so that scurvy may be induced in infants fed entirely on such food. Holst and Fröhlich caused fatal scurvy in guinea-pigs by feeding on barley, oats, or rye. Timely addition of fresh potatoes, apples, carrots, or cabbages, would cure the disease.

Recent observations have shown that although dried products, such as beans and peas, have no vitamin, they develop them if they are damped and allowed to sprout, and are then as effective as fresh vegetables.

Cabbages appear to be by far the most efficient anti-scorbutics, but all the cruciferæ—such as watercress, mustard, turnip, swede, cauliflower, radish, and horse-radish—have that property.

The juice of raw swedes is particularly useful for babies fed on dried or sterilized milk, when oranges or lemons are too dear.

As Hutchison says, this new information should confirm our belief in a mixed diet, drawn from as many sources as possible, and should discourage fads, extremes, and one-sided views and practices in dietetic matters.' It may also have an important bearing on the dietetic treatment of malignant disease (Copeman) as the rapid and disordered growth here may demand more of such substances than normal tissues. Funk found that chickens fed on red rice did not grow. If yeast or powdered sarcoma cells were added, they grew, though not so much as on their ordinary diet.

Calcium Metabolism

Special interest has been taken in the rôle of calcium in the body, and many theories, not always well founded, have been based thereon. Some interesting therapeutic results have, however, been obtained.

In one sense, calcium may be regarded as a very inert substance, as it is deposited in largest amounts in normal tissue with a sluggish metabolism, such as bone, or in any dead tissue which is not infected, but is so large or so situated that it cannot be absorbed. The percentage of calcium may be almost exactly the same in either case. Muscles showing the reaction of degeneration contain an excess of calcium salts, as do retrogressing malignant tumours. Degenerated or necrotic ganglion cells of the brain become infiltrated with calcium salts until a complete cast is formed, with dendrites and axis cylinder infiltrated alike (Wells). Calcification in quiescent tuberculous masses and the deposit of calcium in areas of fat necrosis illustrate the same thing.

The replacement of elastic tissues by calcareous material is a characteristic feature of growing old and is well seen in arterial degeneration, which is in a sense a form of premature senility.

The part played by calcium in the clotting of blood—a change which signifies its death as a tissue—might be regarded as another example, but the calcium only renders the fibrin ferment active, and does not form an essential part in the resulting clot.

But all the activities of calcium cannot be disposed of so summarily; for calcium salts are essential to the heart-beat, and indeed, if they were simply inert, no bad result would follow their removal from the diet. But calcium is constantly leaving the body in the excretions, and it must be replaced. Not only is it excreted in the urine, but Voit found that it was also eliminated by the bowel in small amounts—about 0·15 to 0·16 gramme a day. Some consider the excessive drain of calcium salts in diabetes as a factor in producing acid intoxication. This all points to an active function for calcium salts in metabolism.

A good deal of work has been done on the influence of the ductless glands on calcium metabolism, and Vines' work on the effect of parathyroids in increasing the ionizable calcium content of the blood has been referred to in Chapter I. The usual result of thyroid excess is to increase the excretion of calcium, preventing it from being fixed in the tissues or reaching a high level in the blood. Hence perhaps the menorrhagia common in hyperthyroidism. Excess of the internal secretion of the ovary is said to act in the same way. In osteomalacia there is an abstraction of calcium from the bones. The disease is greatly aggravated by pregnancy, which is attributed to the drainage of calcium from the tissues for the benefit of the fœtus. Removal of the ovaries has been consequently performed, with temporary improvement. Bossi, of Genoa, has found that suprarenal extract, and Blair Bell finds that extract of the pituitary infundibulum, have a similar effect.

Removal of the thymus is followed by increased excretion of calcium (Bosch) and by softening of the bones (Bracci). The influence of the parathyroids on calcium metabolism in relation to tetany and sepsis has been considered already in Chapter I.

Lime-salts are absorbed with difficulty, and appear to retard also the absorption of the fluid in which they are dissolved. The most striking effects of altering the calcium content of the diet are found in connection with the curdling of milk and the clotting of blood; these will therefore be dealt with first.

Calcium and the Curdling of Milk.—The curdling of milk takes place in two stages: first, the rennin of the gastric juice converts the caseinogen into soluble casein; then the calcium salts present precipitate the casein in a soluble form. If the calcium salts be removed, this precipitation does not occur.

Now, in the feeding of infants on cow's milk, one of the disadvantages is that the curd is tough and massive, quite unlike the much finer flocculi formed in human milk. As cow's milk is richer in proteins than human milk, this can be remedied to a certain extent by dilution; but in that case the carbohydrates and fats are reduced too much. Simple dilution may thus mean undernutrition. This can be corrected by addition of sugar and cream, but the method is a little troublesome, and does not altogether avoid the objectionable formation of a tough curd.

Cow's milk contains six times as much calcium as human milk, so if we can remove some of this we

need not dilute the milk so much. Oxalates and fluorides, which were first used to precipitate calcium, are poisonous, and cannot be used. Wright found that citrates, which are harmless, had a similar action. According to C. J. Martin, citrate of soda acts by forming a double salt with calcium, which is not available for curdling of milk or clotting of blood. This has the additional advantage that the calcium not being removed entirely is still available for other purposes in metabolism.

If 3 grains of sodium citrate be added to each ounce of milk, there is only a very fine curd; and 2 grains, or even 1, will markedly diminish its cohesion. The sodium salt is more effective than the potassium salt. The method is simple, for the salt is freely soluble, and the required amount can be prescribed in a drachm of water, to be put in each feed of milk. A little chloroform water should be added to a bottle that has to last a week, to prevent fungus growing in the dilute solution.

In such doses it scarcely alters the taste of the milk at all, and, as it is a neutral salt, it does not tend to inhibit gastric secretion as do the alkaline salts.

Poynton sums up its advantages as follows: It renders the curd of cow's milk more easily digestible; it is cheap, convenient to handle, easy to control, and progressive in principle. It allows the milk to be given in a more concentrated form, and thus avoids to some extent the risk of underfeeding; there is no danger of scurvy; it gains the confidence of the mother,

who naturally believes in medicines. Besides employing it in dyspepsia, he uses it as a routine for weaning a healthy infant on to cow's milk, gradually diminishing the amount of citrate. He does not find it of value in the rare cases of complete intolerance of cow's milk, in severe cases of gastro-enteritis from impure milk, or in organic diseases, such as congenital hypertrophic stenosis of the pylorus. In the last case, however, I think it may be a useful adjunct to other methods, as it is essential to prevent the formation of any lumps in the stomach.

It is called for whenever undigested curds appear in the stools. Apart from other reasons to be considered presently, it should be used in typhoid fever in such circumstances. Our treatment of this disease is often fallacious in that we regard too much the condition of the food when it enters the mouth, rather than its condition as it passes over the ulcers; it is clear that many solid foods are fluid by that time, while milk, though liquid when swallowed, will form curds that may irritate the ileum.

The practical success of this method raises doubts as to the physiological advantages of curdling in general. It is usually claimed that, did curdling not occur, the milk would pass along the intestine too rapidly, and thus escape unabsorbed; but, as a matter of fact, we find that milk may be absorbed more completely when it is thus prevented from curdling. Pancreatic juice contains a milk-curdling ferment, but if the juice be active no curd is seen, because the trypsin

will digest it as fast as it forms. On the addition of 6 per cent. sodium chloride, tryptic activity is delayed and there is obvious curdling. Thus a regulating mechanism is provided, which delays the onward passage of the milk should pancreatic digestion be enfeebled, strongly suggesting that, as long as this is active the formation of a curd has no particular advantage. At any rate, the frequency with which I have seen tough cheesy masses in the stomachs of infants post mortem has impressed me with the accompanying drawbacks.

Calcium and the Clotting of Blood.—In the clotting of blood, the part played by calcium is different. Fibrin ferment results from the interaction of three substances—thrombogen in the plasma; thrombokinase contained in all tissue cells, including the leucocytes and platelets; and calcium salts. Once the ferment has been formed, the calcium can be removed without interfering with the clotting. Thus it operates at an earlier stage than in curdling.

Wright has observed the rate of coagulation by means of a capillary tube, into which the blood is drawn, and the time required for clotting noted, hoping in this way to control the effect of therapeutic measures. If coagulation be too quick, the blood could be decalcified by giving citrate of soda; if too slow, calcium salts could be added.

Addis (*Quarterly Journal of Medicine*, vol. ii., p. 149) seriously questions the accuracy of Wright's method, and therefore of his deductions. While admitting the force of his criticisms, we must recognize that certain

conditions are benefited by giving citrates, and others by calcium salts.

Indications for Decalcification.—Wright asserts that every adult patient who is put upon a diet of milk is thereby predisposed to thrombosis, in consequence of the large intake of calcium salts. He believes this accounts for the frequency of thrombosis as a sequel of typhoid fever. F. J. Smith also thought that he greatly diminished the frequency of thrombosis in typhoid fever by allowing a more liberal and not exclusively milk diet.

Thrombosis occurred, with special frequency, as a sequel to typhoid fever in the South African War.* The usual explanation given was that prolonged marching had thrown a strain on the veins of the leg, but as thrombosis is such a late event in the disease, this must have lost its effect during the long enforced rest that preceded the clotting. It seems to me much more likely that the general use of condensed milk played an important part. Fresh milk contains some citric acid, thus providing the antidote to some of its abundant calcium. This citric acid is apt to separate out in an insoluble form from condensed milk.

In all cases where milk diet is used for some time citrate of soda should be added unless a septic focus is present, which would tend to reduce the calcium

* About 6 per cent. of all cases developed thrombosis, or double the proportion of the cases which do so in this country. Crombie's oft-quoted figures in which 25 per cent. suffered from thrombosis are vitiated by the fact that many of his cases were those invalided home on account of this complication.

content of the blood. Such a simple procedure would justify itself if it saved one patient from the dangers, pain, and chances of lifelong inconvenience entailed by thrombosis.

When once clotting has occurred in a vein, the question arises whether it is better to give citrates with the view of aiding resolution, or calcium salts to assist in getting the clot as firm as possible and thus diminishing the risk of embolism. Of late the tendency has been to administer parathyroid extract with calcium salts with the latter object.

Indications for Increasing Coagulability.—Wright's attention was drawn to this subject because as a boy he was subject to severe giant urticaria when he took acid fruits, which are, of course, rich in decalcifying agents. Chilblains, 'angio-neurotic' œdema, and physiological albuminuria, he considers to be, like urticaria, due to lowered coagulability of the blood, which permits transudation of plasma from the vessels into the lymph spaces—a 'serous hæmorrhage,' as he calls it. Gewin found that serum sickness was much less common if calcium salts were given by the mouth at the time antitoxin was injected. The bearing of this on functional albuminuria has been referred to in Chapter VIII. In all these conditions the blood must be replenished with those salts which render the plasma more coagulable and viscid.

For this purpose calcium lactate has yielded the best results. This salt has the following advantages: firstly, it is devoid of unpleasant taste, is suf-

ficiently soluble (about 1 in 10) in water, and is suitable for administration in the form of powders; and, secondly, as the salts of organic acids, and more particularly of lactic acid, are readily oxidized in the body, their bases are more readily utilized. A dose of 4 grammes (1 drachm) may increase the coagulability of the blood within twenty minutes, and maintain its effect for from four to seventeen days. It should be given when it is desired to exalt coagulability as rapidly as possible. When the object is to maintain a permanently high level of blood coagulability, the dosage should be 1 gramme (15 grains) three times a day.

Magnesium salts bring about a similar change, which explains the rationale of magnesium carbonate in the treatment of urticaria, and its special efficacy in that form of urticaria which follows upon the ingestion of decalcifying agents.

Calcium salts are used with the intention of promoting clotting in the sac of an aneurism, in purpura, hæmophilia, intestinal hæmorrhage, and as a precautionary measure against bleeding during operations, but I have not been impressed with the results. Cushing doubts whether any improvement observed in such cases can really be referred to the drug, since much more calcium is taken in with the food than is sufficient for the body. On the other hand, Addis, though denying that the coagulation-time is increased, admits that the amount of ionizable calcium in the blood can be increased by the administration of soluble calcium salts.

G. W. Ross met with severe chronic headache, troublesome urticaria, and deficient coagulability of the blood in a patient. Calcium chloride was given for the urticaria, and the headaches vanished also. This suggested to him that the headache might also be due to a similar 'serous hæmorrhage' into the meninges. He treated forty-eight cases with 15 grains of the chloride or the lactate of calcium three times a day. Forty of the cases obtained complete relief and eight considerable relief. With the relief, the coagulability of the blood was exalted in all the cases in which it was tested. According to him the type of headache which responds to this treatment presents the following characteristics:

1. It is present and most severe on waking, and tends to disappear one to six hours later.

2. It is usually a dull, heavy ache or a frontal or temporal throbbing; occipital, vertical, or unilateral pain being less common.

3. It is very chronic, often of several years' duration, and most intractable to ordinary treatment.

Women are more frequently affected than men. The expression is heavy and listless, the face is full, and the eyes are often puffy. Some anæmia is usual; constipation is the rule; loss of appetite and indigestion are common. There is a tendency to chilblains, urticaria, and œdema, the latter manifesting itself more commonly as a morning fulness between the eyes, and less frequently as an œdema of the ankles and feet. The patient sleeps heavily, but wakes without feeling

rested, and there is a tendency to mental depression. Irritability combined with languor he regards as characteristic.

He found the symptoms returned on decalcification of the blood by sodium citrate to disappear a second time on treatment with calcium lactate. I have seen an example of this type of headache with menorrhagia (which also is associated with low calcium content) greatly benefited by calcium lactate.

Calcium and the Rhythm of the Heart.—In the chapter on irregular action of the heart it was shown that calcium salts were essential to cardiac systole. Howell and Duke found that increase in the concentration of calcium salts acted like stimulation of the accelerator nerve. There was chiefly augmentation of the beat. A reduction in the calcium salts caused a more rapid as well as a more feeble beat. In the total absence of calcium the heart does not beat, though the electro-cardiogram shows that the metabolic changes still continue.

Calcium has accordingly been used as a heart tonic in pneumonia; but it has not been an invariable success, and has sometimes been followed by thrombosis—not an uncommon accident in this disease. It is, indeed, a two-edged sword in the treatment of circulatory failure, because of its liability to provoke clotting.

Calcium Salts and Metabolism of Bone.—Deficiency of lime in the food affects the young more than adults, since the former require more for the forming of the skeleton. Puppies fed on a diet poor in calcium suffer

from deficient growth of the bones. Pigeons thus dieted exhibit fragility and atrophy of the bones. Lime starvation, however, merely causes an imitation of rickets, because the bone cells, though still ready to deposit calcium, cannot obtain it.

Calcium and the Puerperal State.—The drainage of calcium into the blood and its passage into the fœtus during pregnancy have already been referred to. Coagulation time is consequently reduced. As Blair Bell suggests, the cessation of the periods may be a factor in keeping the calcium content of the blood high at this time. Winckel finds that the blood then has a somewhat diminished alkalinity, which would enable it to hold a larger amount of calcium in solution.

Immediately after delivery blood clots rather more quickly than normal. As suckling begins, coagulation becomes perceptibly slower from the drainage of calcium salts into the milk. Hingston Fox suggests that observation of the coagulation time of the blood after delivery might give timely warning of the risk of thrombosis or embolism if it were quick, or of post-partum hæmorrhage if it were slow. Appropriate treatment, with citric acid on the one hand, or with calcium lactate on the other, might help to rectify this.

Eclampsia has also been referred to a drainage of calcium salts from the mother to the fœtus, but probably on inadequate grounds.

Other Effects of Calcium Salts.—Deficiency of calcium salts in the saliva may be a factor in dental

caries. They are most abundant in the parotid saliva, hence the back teeth are apt to decay first in such cases.

Many of the other therapeutical applications of calcium salts depend either on their physical state—as, for instance, the use of chalk as an astringent—or on their alkalinity, and do not, therefore, concern us here. The usefulness of a decalcifying agent in oxaluria has already been explained.

The Allied Metals, Barium and Strontium.—Barium is the most poisonous metal of the group. It is very slowly absorbed from the bowel, and may excite vomiting and purging, with very active peristalsis. It is incapable of replacing calcium in its relations to living matter, and is not nearly so efficient in maintaining the rhythm of the excised heart. According to some observers, it can replace calcium to a limited extent in the coagulation of the blood. It has been used principally for its effect on the cardio-vascular system. The waters of Llangammarch Wells owe their reputation in the treatment of heart disease largely to the barium they contain. Like digitalis, barium causes the frog's heart to beat more slowly, but more strongly, and it produces a rise of blood-pressure by constriction of the bloodvessels. The use of the insoluble and inert barium sulphate in X-ray examination is more economical than bismuth, and almost as effective, but is based on purely physical considerations.

Strontium is the least poisonous of the three, being comparatively inert, even when injected directly into

the blood. Like the others, it is absorbed very slowly from the bowel. It can replace calcium more or less perfectly in its influence on the heart-beat. It has been used chiefly for its anion, in the form of strontium bromide, for epilepsy; but, as it is absorbed so much more slowly than the corresponding salts of sodium or potassium, it is usually less satisfactory for this purpose.

Antagonism of Calcium to Magnesium.—Although magnesium salts, like calcium salts, according to Wright, can exalt the coagulability of the blood in appropriate doses, these two metals are generally antagonistic in their effect on the tissues. Meltzer and Auer showed that the intracerebral instillation of two or three drops of a solution of magnesium sulphate produced a peculiar paralysis in rabbits, while injection of other salts was either indifferent or caused convulsions. The subcutaneous or intravenous injection of magnesium salts caused a general anæsthesia with paralysis, in which the reflexes were abolished and the blood-pressure was lowered. With a dangerously large dose, respiration ceased, the heart usually continuing to beat for some time longer. But as long as there were some efficient heart-beats and a few respiratory gasps, the intravenous injection of a calcium salt, such as the chloride or the acetate, infallibly improved the respiration at once, and quickly revived the animal.

Magnesium favours inhibitory processes in the body, and in this it is definitely antagonized by calcium.

This inhibitory action of magnesium suggested its use in the treatment of tetanus. It can have no action on the toxin, but by controlling the spasms it keeps up the patient's strength, and gives him time to form his own antitoxin. The results have been encouraging. Most of the recorded cases have been treated by subarachnoid injections, but Peter Paterson (*Lancet*, 1910, vol. i., p. 922) has reported a successful example of its subcutaneous use. At first 10 c.c. of a 10 per cent. sterilized solution of magnesium sulphate were injected every four hours for two days; later 20 c.c. were similarly injected for four days. The great objection to the method is the pain produced by the injections, but probably this could be mitigated by using larger quantities of a more dilute solution.

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